Clinical and Pharmacological Effects of Substance BZ-55 in Diabetes

(p-Aminophenylsulfonyl Butylcarbamide)

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Two orally administered preparations having hypoglycemic action in the diabetic patient have been under study by a number of investigators in this country for the past year. The compound utilized in these studies has the chemical structure shown in figure 1 and has been given the generic name of carbutamide.

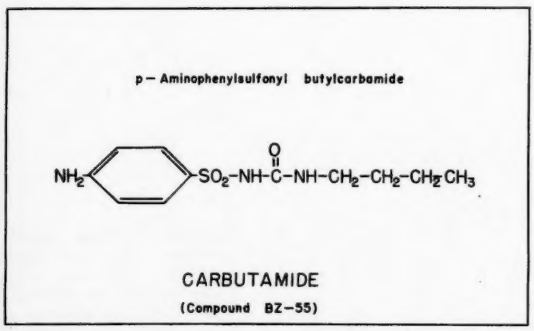

FIGURE 1

The hypoglycemic effect of sulfonamide derivatives is actually not a new observation since this action was first reported by Janbon[1] in 1942. He noted hypoglycemia while studying the antibacterial action of sulfonilamido isopropylthiodiazole. In 1944 Loubatieres[2] found that this same compound was without action in the depancreatized dog and postulated that hypoglycemia in the normal animal was probably the result of a stimulation of insulin secretion.

In 1946, Chen et al.,[3] showed that the cyclopropyl derivative lowered blood sugar profoundly in normal rabbits following 1- to 2-gm. doses orally, but in the alloxan diabetic rabbit a marked increase in blood sugar occurred. It was felt that these results were in agreement with Loubatieres' and perhaps indicated stimulation of insulin secretion.

In 1955 Achelis and Hardebeck,[4] Franke and Fuchs,[5] and Bertram, Bendfelt and Otto,[6] published experimental results with p-aminophenylsulfonyl butylcarbamide, designated compound BZ-55. They showed that the blood sugar could be lowered in normal animals and in certain diabetic patients. Franke and Fuchs[5] suggested on the basis of animal experimentation that the action of the drug might be due to an effect on the alpha cells of the pancreas with a resultant inhibition of glucagon production. Ferner[7] did not find that degranulation of alpha cells could be demonstrated in one patient given BZ-55.

The compound has been under study in this country since July 1955 and this report includes the results of acute and chronic toxicity in animals, of some of the effects of carbutamide in normal and diabetic animals, and a brief summarization of the effects in the treatment of diabetic patients.

ACUTE TOXICITY

The acute toxicity in normal animals is low. The LD_{50} of intravenously administered drug in mice is 1.9 gm./kg. Orally, the LD_{50} is 3.5 gm./kg.

Although some hypoglycemia occurred during the toxicity studies, death was not due to low blood sugar. Blood glucose levels were 104 to 122 mg. per cent just before death in rats; furthermore, the administration of

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glucose intraperitoneally 5 to 10 minutes before the intravenous dose of carbutamide did not alter the LD_{50} or change the toxic reaction.

Hypoglycemia can be produced in rabbits following single doses of 50, 100, and 150 mg./kg. intravenously, and with each increase in dosage, a fall in blood sugar of greater degree and duration is produced.

Carbutamide administered orally to rabbits varied greatly from one animal to another in its hypoglycemic effects. A single 500 mg./kg. dose may produce only a moderate fall in blood sugar in one animal, yet cause convulsions and prostration in another and require either glucagon or glucose to reverse the severe hypoglycemia.

In normal dogs doses up to 700 mg./kg. orally produce only a slight decrease in blood sugar. Seven hundred to 1,000 mg./kg. as a single oral dose caused vomiting and muscular weakness and twitching. Hypoglycemia did not develop and glucose did not relieve the symptoms.

CHRONIC TOXICITY

At the end of five months, rats fed diets containing 0.25 per cent and 0.5 per cent carbutamide have all survived and have shown normal weight gain.

Deaths occurred in two out of ten rats fed 1.0 per cent in the diet after 33 and 121 days respectively. Blood carbutamide levels ranged between 30 and 60 mg. per cent. On a diet containing 2 per cent of drug, all animals were dead by 205 days. The first of this group died after

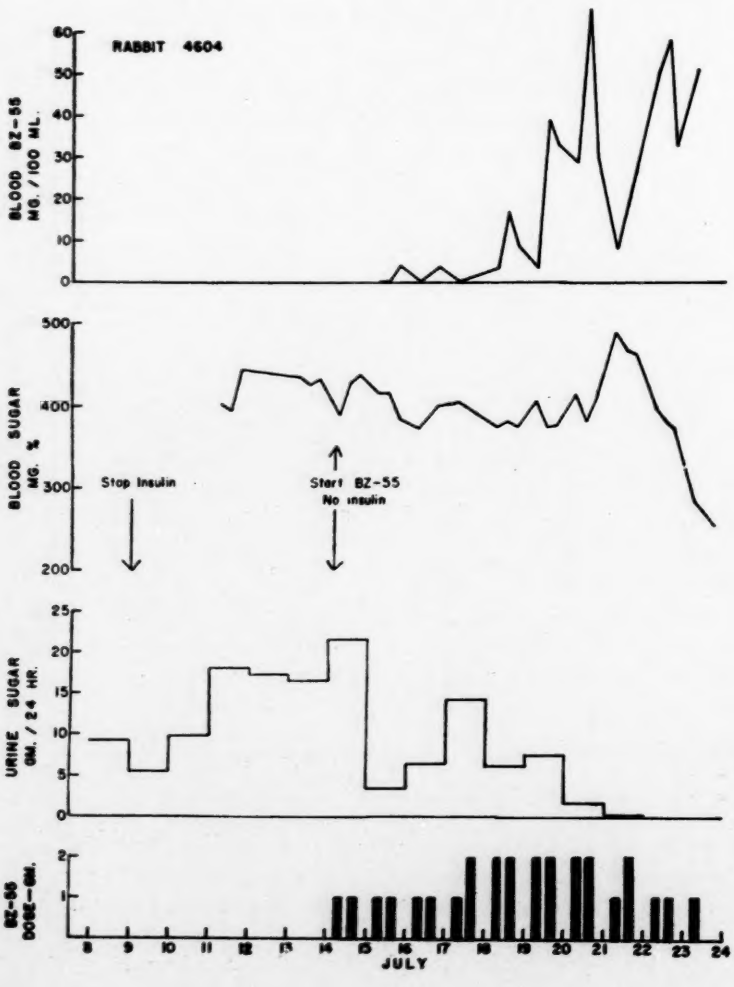

FIG. 2. Alloxan diabetic rabbit treated with carbutamide (BZ-55). The drug was administered by stomach tube twice daily in doses indicated by vertical bars. Progressive diminution of food consumption during treatment period contributed to the fall in blood sugar and glycosuria.

29 days. Blood carbutamide levels were more than 70 mg. per cent.

Postmortem examinations of the twelve rats that died while on the drug revealed various lesions. Malnutrition was present in all animals. Crystalluria was found in four, and central necrosis of the liver was observed in only one. Hypertrophy of the thyroid of a slight degree was observed in half the animals which had received the 2 per cent diet.

In monkeys, daily doses of 250 mg./kg. by stomach tube were tolerated well and all animals maintained or gained weight. Blood carbutamide levels reached a peak of 45 to 65 mg. per cent two hours after each dose and fell to a trough value of 4 to 12 mg. per cent.

A fall in blood sugar was noted following each dose although the pattern was inconsistent from day to day.

Urinary excretion of the drug shows a species variation. Rabbits excrete the acetylated form to the greatest degree. Dogs excrete the free form for the most part and in man the excretion is intermediate, approximately 66 per cent of the free form and 33 per cent as the combined form.

EFFECTS ON DIABETIC ANIMALS

To study the response in experimentally induced diabetes, alloxan diabetic rats, rabbits and dogs, and depancreatized dogs were treated with carbutamide. Alloxan treated rats showed no improvement in the diabetic state when carbutamide was administered daily in doses up to 1 gm./kg. orally.

In an alloxan diabetic rabbit (figure 2) there was no decrease in blood sugar until the last few days, at which time the animal had stopped eating and was in poor physical condition. Urinary sugar excretion decreased slightly with decrease in food intake and fell off to zero when the animal stopped eating entirely.

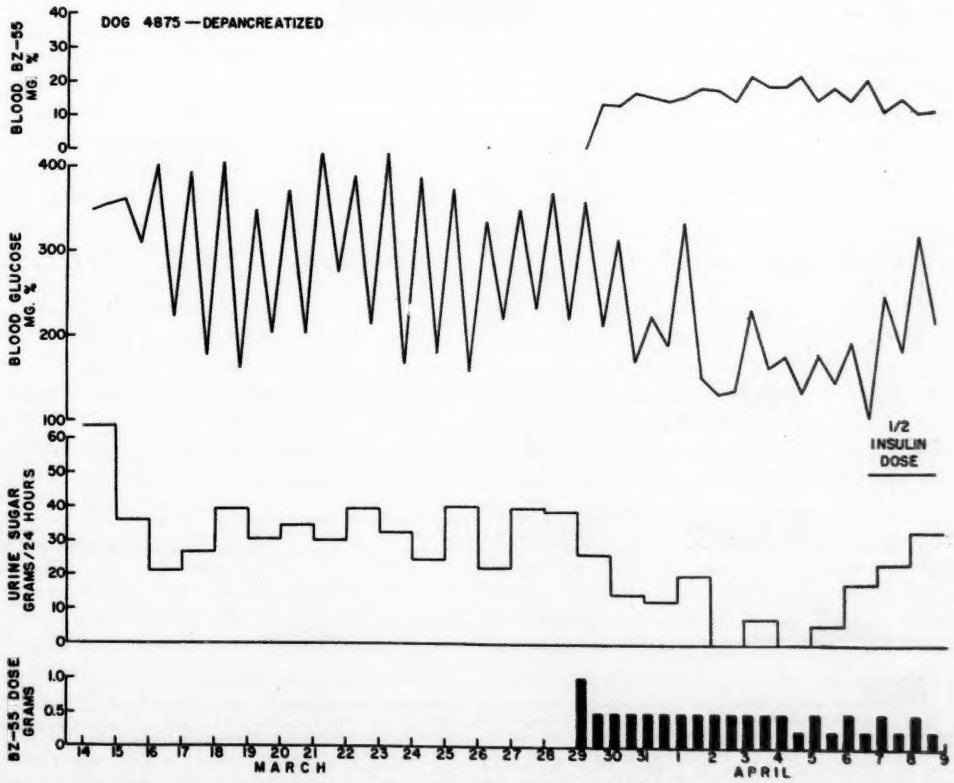

FIG. 3. Totally depancreatized dog poorly controlled on a constant dose of NPH insulin and a constant diet. Carbutamide was administered orally as indicated. With no change in insulin or diet there was a fall in blood sugar and glycosuria. During the last two days of the experiment the insulin dose was decreased by one-half with a return of glycosuria.

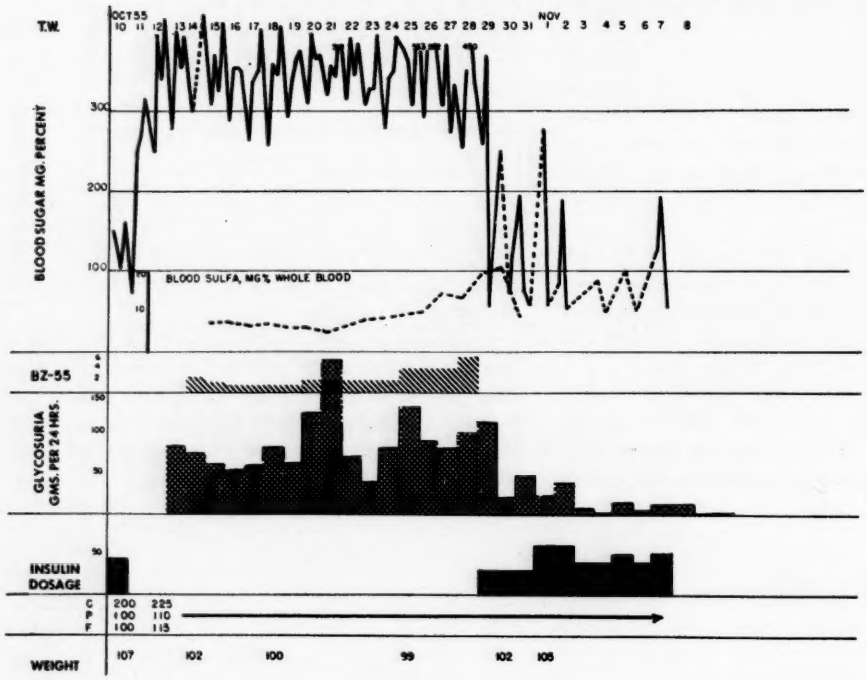

FIG. 4. Asthenic male patient age thirty - eight. There was a complete lack of response to carbutamide. Rapid improvement followed reinstitution of insulin therapy.

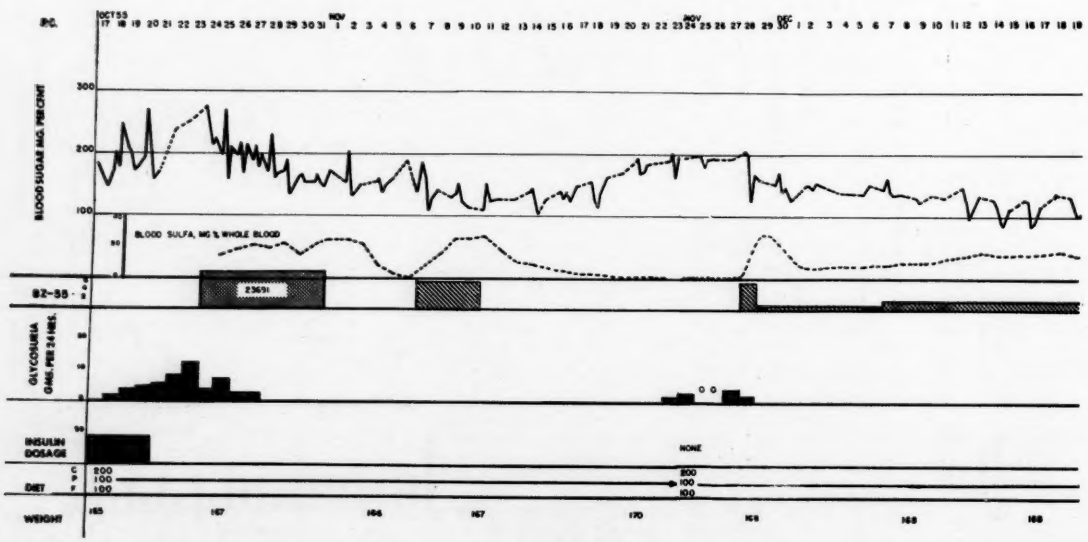

FIG. 5. Obese female patient age fifty-nine previously well controlled on 40 units of insulin daily. A gradual lowering of blood sugar is demonstrated following the use of sulfonamide derivatives. She continues to be well controlled on 2 gm. daily and no insulin.

A totally depancreatized dog, maintained on unmodified insulin, showed a drop in blood sugar when carbutamide was given orally, eighteen hours after the last dose of insulin. This same animal showed no response when carbutamide was given sixty-six hours after the last insulin dose. Apparently some unmodified insulin still remained in the animal's tissues after eighteen hours.

It seems clear that insulin or functioning islet tissue must be present if a hypoglycemic response to carbutamide is to be expected.

Data which indicate that there may be an effect on insulin activity are demonstrated in the following experiment (figure 3).

A totally depancreatized dog on a constant, weighed diet and receiving suboptimal doses of insulin, showed a reduction in daily excretion of glucose when carbutamide was added to the regimen. Indications are that approximately one-half the dose of insulin was replaced in this particular animal.

CLINICAL STUDIES

Up to the present time, fifty patients have been treated with carbutamide at the Lilly Laboratory for Clinical Research and the Indianapolis General Hospital Outpatient Diabetic Clinic. Twenty-two of this group were started directly in the outpatient clinic and were not hospitalized for stabilization.

Following earlier questionable results in patients with long standing, severe diabetes, a better selection of the group to be treated was accomplished and success in lowering blood sugar and reducing glycosuria was obtained in the majority of patients.[8]

Generally, this latter group of patients have had diabetes of the maturity-onset type, which is relatively mild, and have either required no insulin in treatment or have taken a small daily dose.

Exceptions to this general classification have been found, which is doubtless the experience of all who have tested the drug.

Initially, six grams per day of carbutamide was used, a dose far higher than necessary. Later the dose was lowered to that recommended by the German investigators, namely, 2.5 gm. the first day, 1.5 gm. the second and 1 to 2 gm. daily thereafter. If a patient does not respond to this dosage, it is unlikely that a higher dose will be effective. Blood carbutamide levels have ranged from 4 to 17 mg. per cent and there does not seem to be good correlation between blood level and clinical response. Many patients showing good blood sugar lowering effects have had consistently low blood carbutamide levels.

Certain patients respond poorly or not at all to carbutamide. Figure 4 demonstrates graphically an example of a total failure. This patient, a thirty-eight-year-old, asthenic male who had been in acidosis and coma several times showed immediate deterioration of his diabetic status as soon as insulin was stopped and carbutamide started. He responded promptly when insulin therapy was reinstituted.

Patients who respond may follow one of two patterns of hypoglycemic effect. First there may be a quite rapid lowering of blood sugar to normal levels, most commonly seen in newly discovered diabetics or in patients who have never received insulin. The second pattern is a slower lowering of blood sugar over a period of days as demonstrated in figure 5. This patient first received the propyl analogue of carbutamide but later received carbutamide itself. Since her release from the hospital she has continued to do well on the drug as an outpatient.

This next example is that of a patient in whom a good hypoglycemic response was obtained but in whom toxic effects were observed (figure 6). Thirty-one days after the initiation of therapy the patient complained of a rash and was found to have a depressed white cell count. It was felt that perhaps high dosage may have contributed to the development of the sensitivity since she had received six grams of the drug daily on two different occasions and had shown a maximum blood carbutamide level of 35 mg. per cent. Symptoms disappeared rapidly when the drug was stopped. It is imperative that all patients have regular periodic white blood counts and if any evidence of agranulocytosis or other abnormality of the blood develops, the drug should be stopped immediately. Patients started on carbutamide in the outpatient clinic have had weekly white blood counts until they are stabilized on dosage. Later they are seen at monthly intervals and repeat counts are routine. Undesirable side reactions do exist and they must be guarded against.

Two points of chief interest are now receiving maximum attention. Firstly, how hypoglycemia is achieved and whether the diabetic is actually benefited by this action, and secondly, whether deleterious effects result from long-term administration of the compounds.

Since alpha cells and glucagon had been implicated, a group of six mild diabetic patients who showed a blood sugar response to carbutamide were given glucagon tolerance tests before and after receiving carbutamide. These same patients also were given glucose and insulin tolerance tests before and after carbutamide. These results are shown graphically (figure 7).

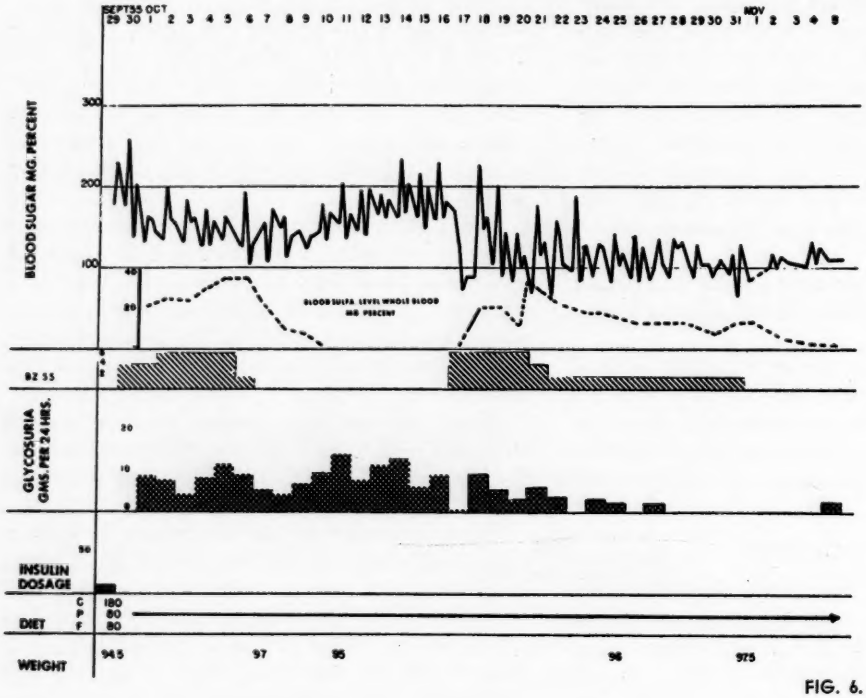

FIG. 6. (Above) Asthenic female patient age fifty-four with mild diabetes requiring 10 units of insulin daily. She showed stabilization on 2 gm. of carbutamide daily after two previous poor responses to 6 gm. daily. Patient was found to have a rash and leukopenia at the thirty-first day of regimen, and the drug was stopped.

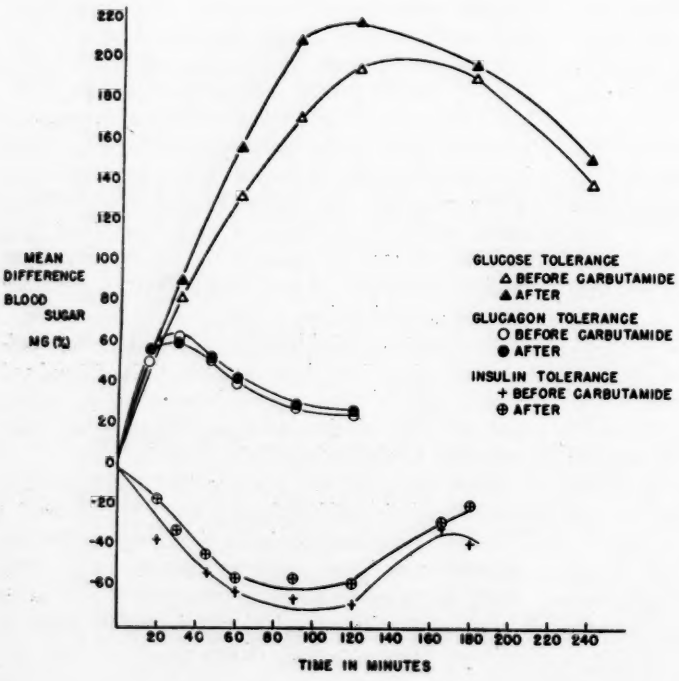

FIG. 7. Glucose, glucagon, and insulin tolerance tests in six mild diabetic patients who showed hypoglycemic response to carbutamide. No significant differences in the curves before and after carbutamide therapy were demonstrated.

These data have been subjected to statistical analysis and it is concluded that by the methods utilized, no significant differences could be found attributable to the carbutamide.

Because of evidence in animals indicating possible undesirable effects on thyroid, renal, and liver function, groups of patients taking a therapeutic dose of carbutamide have been investigated to determine if significant effects are present in patients as well.

Thyroid function as measured by I^{131} uptake, protein bound iodine determinations and basal metabolic rate, has remained normal in ten cases. Forty of the group have had serum transaminase studies as a liver function test while on the drug and there was no evidence of liver damage. All other tests of liver and renal function have remained within normal limits. Not a single example of crystalluria has occurred. White blood counts have remained unchanged in all but one patient who showed a transient leukopenia.

SUMMARY

Carbutamide and related compounds will lower blood sugar in normal animals and in normal and diabetic patients. In addition, glycosuria is diminished in diabetic subjects.

Experimentally, it has been shown that endogenous (or exogenous) insulin must be present for a blood sugar lowering effect to occur. Clinically, the best response to carbutamide can be anticipated in the obese patient with mild diabetes of short duration. Juvenile patients with diabetes of several years standing and severe, easily decompensated patients respond poorly or not at all.

Although toxicity in normal animals is low, there is suggestive experimental evidence that thyroid, renal, and liver function may be altered. Clinically, such effects have not been demonstrated in this study.

Sensitivity reactions such as skin rash and leukopenia, although infrequent, occur relatively early in the course of therapy. In our opinion, these reactions are definite indications for stopping the drug. Nothing as yet is known of the effects of long-range chronic administration of this compound.

So far, no single theory of mechanism of action is completely satisfactory in explaining all reported effects of these substances on carbohydrate metabolism.

SUMMARIO IN INTERLINGUA

Effectos Clinic e Pharmacologic de p-Aminophenylsulfonyl-Butylcarbamido (Substantia BZ-55) in Diabete

Carbutamido e compositos affin reduce le nivello del sucro sanguinee in animales normal e in patientes normal e diabetic. In plus, illos reduce glycosuria in subjectos diabetic.

Il ha essite demonstrate experimentalmente que le occurrentia de un reduction del sucro sanguinee require le presentia de insulina endogene (o exogene). Le melior responsa clinic a carbutamido es a expectar in patientes obese con leve diabete de breve duration. Patientes con diabete juvenil de plure annos de duration e patientes con sever grados de diabete que es facilemente discompensate responde pauco ben o non del toto.

Ben que le toxicitate in animales normal es basse, il ha datos experimental que suggere que le functiones thyroide, renal, e hepatic es possibilemente alterate. In le presente studio tal effectos ha non essite demonstrate clinicamente. Reactiones de sensibilitate—per exemplo eczema cutanee e leucopenia—esseva infrequente e occurreva relativemente tosto in le curso del therapia. In nostre opinion, tal reactiones es definitivemente indicationes pro le discontinuation del administration del droga. Nulle informationes es disponibile a iste tempore in re le effectos de chronic administrationes a longe durantia.

Usque nunc nulle theoria individual del mechanismo del action del droga es completemente satisfactori, i.e., nulle theoria individual pote explicar omne le reportate effectos de iste substantias super le metabolismo del hydratos de carbon.

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Sulfonylureas and Diabetes Mellitus:

I. Clinical Evaluation

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In the search for orally active hypoglycemic agents, extracts of vegetable substances, bacteria, yeasts, and molds have received limited laboratory and clinical study, but as indicated by Lewis' extensive review[1] none has been satisfactory. Guanidine derivatives[2] gave promise of usefulness but proved too toxic. Interest in sulfonamides began in 1941 when Janbon[3] reported that p-aminosulfonamido-isopropylthiadiazole was hypoglycemic and virtually nontoxic in man and experimental animal. Loubatieres,[4-6] Bovet,[7] Holt,[8] and Chen[9] extended these observations. General interest was not aroused until 1955 when Achelis,[10] Franke,[11] and Bertram[12] reported laboratory and clinical experiences with 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide). This compound seemed to provide adequate substitution for exogenous insulin in a large proportion of diabetics.

Concomitantly, another drug, 1-butyl-3-p-toluenesulfonylurea (tolbutamide), was shown to be hypoglycemic but, unlike carbutamide, did not possess bacteriostatic properties.[13] All available information indicates that these compounds are useful in the treatment of diabetes mellitus, are free from adaptive tolerance, and are infrequently toxic.

In this report are presented clinical studies of the antidiabetic effectiveness of carbutamide and tolbutamide, as well as certain investigations of their actions.

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MATERIALS AND METHODS

Fifty-six diabetic patients were treated with either 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide),* or 1-butyl-3-p-toluenesulfonylurea (tolbutamide).† Thirty four of these patients were hospitalized for the initial portion of our studies of them.

Prior to institution of sulfonylurea therapy, an attempt was made to determine optimum dietary and insulin requirements. The established dietary program for the individual patient remained constant, regardless of whether insulin or sulfonylurea therapy was used. Patients were selected so as to provide representation from all age groups and all varieties of diabetes.

Initial and follow-up laboratory studies consisted of measurements of the hematocrit, reticulocyte count, white blood count, urinalysis, serum creatinine, serum bilirubin, and two-hour postprandial blood sugar. Each patient tested his urine for reducing substances four times daily and recorded the values. Tests were performed weekly for three weeks and biweekly thereafter. Additional laboratory procedures performed in hospitalized patients were: daily twenty-four hour urine sugars, four hourly qualitative urine sugars, blood sugars obtained at 7 a.m., 11 a.m., 4 p.m., 8 p.m., and 2 a.m., bromsulfalein dye retention, thymol turbidity, cephalin-cholesterol flocculation, total serum protein, serum albumin, serum globulin, prothrombin time, and phenolsulfonphthalein excretion. In some patients there were studies of the serum sodium, potassium, bicarbonate, and chloride levels, and of the titratable acidity of the urine.

The initial sulfonylurea was given twenty-four hours after the last modified insulin injection. No further modified insulin was administered, but crystalline insulin

*Kindly supplied by Dr. W. R. Kirtley, Eli Lilly and Company, Indianapolis, Indiana.

†Kindly supplied by Dr. C. J. O'Donovan, Upjohn Company, Kalamazoo, Michigan.

was supplied when fractional urinalyses revealed as much as 2 per cent sugar. In this fashion we were able to evaluate each patient and maintain reasonable diabetic control, regardless of the response to the experimental drug. The drug dosage was variable. Most patients were given 3 gm., 2 gm., and then 1 gm. of the compounds on successive days. The daily maintenance dose was usually 1 gm. If the patient did not respond by the fourth day, the dose was increased, so that some patients received as high as 8 gm. of carbutamide or 6 gm. of tolbutamide daily for short periods of time. All daily doses were divided. Therapy was deemed unsuccessful if after eight to nine days of therapy on increased dosage the diabetes was uncontrolled, requiring supplementary insulin.

Modified intravenous glucose-insulin tolerance, intravenous glucagon tolerance, epinephrine tolerance and intravenous insulin-I^{131} plasma binding tests were performed on certain patients. The methodology is described subsequently.

RESULTS

Of the fifty-six patients participating in the study, 50 per cent were deemed successfully treated. Criteria for success were: (1) twenty-four hour urinary sugar excretion of less than 10 gm., (2) all fractional urinary sugar estimations 0.25 per cent or less, (3) two-hour postprandial blood sugar values of less than 160 mg. per cent, (4) control of acute symptoms referable to diabetes, and (5) a complete lack of distressing side effects of more than transient nature. Twenty-five per cent of the total group were females of whom 43 per cent responded favorably. Seventy-five per cent of the subjects were males, and 52 per cent of these were able to eliminate insulin from their regimen. The duration of the sulfonamide treatment varied from 4 days to 90 days.

Age and Success. The relation of age to successful treatment is depicted in figure 1a. No patient under thirty years responded, whereas the success incidence in all patients over forty was better than that of the total group.

Habitus and Success. Figure 1b shows that endomorphic individuals enjoyed a distinctly higher incidence of success than the others. Eighty-three per cent of endomorphic diabetics responded satisfactorily whereas only 43 per cent and 29 per cent, respectively, of mesomorphic and ectomorphic subjects did well.

Age of Onset and Success. No patient whose disease onset was at age thirty or below responded successfully, as shown in figure 1c. The later the temporal onset the better the response rate. Patients with the onset of diabetes after age forty had a greater incidence of success than did the average subject.

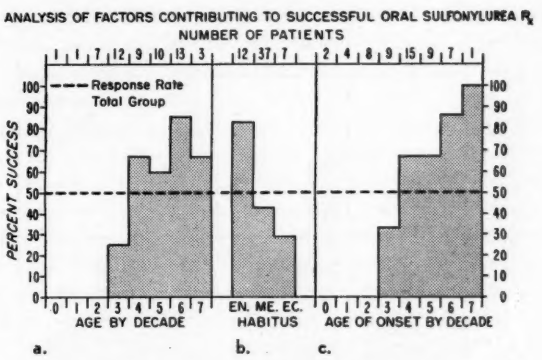

FIG. 1. (a) The relationship of age to treatment success. (b) The relationship of habitus to successful treatment. Endomorphic patients responded better than mesomorphic or ectomorphic ones. (c) No patient whose disease began prior to age thirty responded to treatment.

Duration of Diabetes and Success. Duration of diabetes played a prominent role in ultimate success. Figure 2a illustrates that 73 per cent of patients who had a history of the disease for less than one year responded. Subjects whose disease ranged from one to five years in duration demonstrated 61 per cent success. Those with diabetes longer than five years did less well than the group as a whole.

Duration of Insulin Therapy and Success. Figure 2b demonstrates that patients who had received insulin for less than one year, or not at all, had a much greater success rate than those receiving hormone replacement for greater periods of time. Seventy-eight per cent of subjects in the one year or less category did well. Beyond that period, duration of insulin treatment made little difference in the incidence of success, with 38 per cent responding in the one to five year group, 40 per cent in the five to ten year category, and 30 per cent in the ten year plus subdivision. It should be mentioned that all successful patients in this latter category were of maturity-onset type.

Pretreatment Insulin Requirement and Success. All patients requiring less than 30 units of insulin per day responded better than the general group as exemplified in figure 2c. One hundred per cent of the very mild diabetic patients who required 10 units of insulin or less daily attained excellent control with sulfonylurea treatment.

Complications and Success. Complications of diabetes mellitus were present in 25 per cent of the patients. No

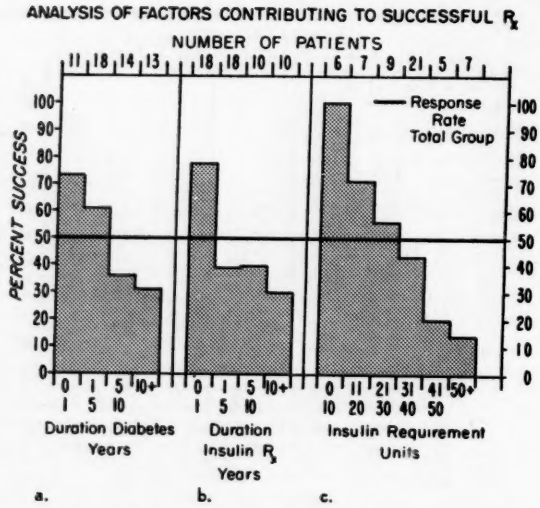

FIG. 2. (a) The relationship of duration of diabetes to successful treatment. (b) Patients treated with insulin for longer than one year respond less well than the group as a whole. (c) If the insulin requirement of the patient is less than 30 units, the patient will respond better than the average of the group.

subject with severe cardiovascular-renal disease responded favorably. The incidence of neuropathic or cardiovascular-renal disease of mild degree played no role in success or failure, as 25 per cent of the favorably responding group had such disorders.

Choice of Drug and Success. Thirty-one patients were treated with carbutamide, and in 39 per cent the diabetes was controlled adequately. Five patients were unable to continue the medication because of gastrointestinal disorders, probably not related to drug ingestion; if these five are deleted, then 46 per cent responded satisfactorily. Twenty-five patients received tolbutamide and yielded a 60 per cent success rate.

Toxicity and Side Effects. Careful clinical and laboratory follow-up has revealed no objective toxicity to date. Dermatologic lesions have not occurred. In the majority of subjects, appetite and general well-being were not affected and weight remained stable. Distressing side effects were noted by twelve patients. Although nausea was the principal untoward symptom in six of seven patients experiencing this, there were other operative factors present. There was increasingly poor diabetic control in three, viral gastroenteritis in two, and concomitant excessive self-administration of norisodrine in one. One patient noted transient nausea during the first two days of carbutamide administration which did not return despite continued drug ingestion. "Giddiness" associated with poor control caused one patient to cease carbutamide therapy. Drowsiness occurred transiently in one patient during the second and third days of tolbutamide treatment. Extremity paresthesia was reported by two patients as transient events during the first week of tolbutamide therapy. One elderly patient with Parkinson's disease noted an increase in tremor, seemingly associated with tolbutamide administration.

Results in Patients with Additional Disease. Fifty per cent of the patients had other diseases, and of this group 57 per cent responded to the drugs. Included in this group were patients with peptic ulcerative disease, pulmonary tuberculosis, chronic pulmonary insufficiency, chronic alcoholism, myasthenia gravis, Parkinson's disease, degenerative joint disease, early nutritional cirrhosis of the liver, and a patient with surgical pancreatic insufficiency. All of the patients' auxilliary diseases were well-compensated during the study and, with the exception of the Parkinsonian, the patients demonstrated no additional symptoms. The patient with diabetes secondary to total pancreatectomy for insulinomata did not respond to sulfonamide therapy and will be discussed subsequently.

Special Metabolic Tests. Intravenous glucose-insulin tolerance, intravenous glucagon tolerance, epinephrine tolerance, and intravenous insulin-I^{131} plasma binding tests were performed on a number of subjects prior to and during treatment with the sulfonylureas. Base-line testing was accomplished in fasted patients who had not received insulin the morning of the procedure. All patients in this report subsequently received the oral hypoglycemic agents in adequate dosage to control their disease. This was usually a maintenance dose of 1 gm. daily. Five hundred milligrams were given one hour prior to the final tolerance procedures.

a. To determine if the sulfonylureas increased the effectiveness of a given amount of insulin, a modified glucose insulin tolerance test was devised. Twenty grams of glucose in distilled water containing 10 units of crystalline insulin was infused over a sixty-minute period. Blood sugar levels were determined at zero time, 15 minutes, 30 minutes, 60 minutes, and 90 minutes. Figure 3a shows the mean response of six patients. The mean differences are not significant as calculated by the method of significance of difference between two means. This small series suggests that sulfonylureas do not influence the effectiveness of a given amount of exogenous insulin.

b. Inhibition of enzymatic hydrolysis of glycogen can produce hypoglycemia. Glucagon causes hyperglycemia in

diabetics and normal subjects,[14] by stimulating the reactivation of liver phosphorylase.[15] If sulfonylureas inhibited this reaction, then glucagon hyperglycemia would be diminished. To test this hypothesis in successfully treated diabetic subjects, 2.5 μg. of glucagon* per kilogram of body weight, in a vehicle of 150 ml. of 0.9 per cent saline, was administered intravenously over a fifteen-minute period. Blood sugar levels were determined at zero time, 15 minutes, 25 minutes, 35 minutes, and 65 minutes.

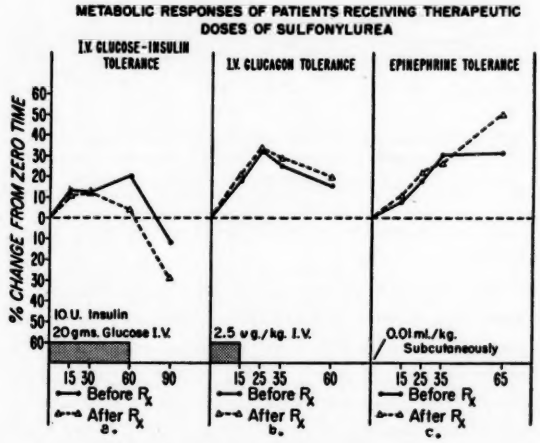

FIG. 3. (a) Sulfonylureas do not increase the effectiveness of insulin. (b) Treatment does not alter the response to glucagon. (c) Epinephrine tolerance is not changed in the presence of therapeutic dosage of sulfonylurea.

Figure 3b illustrates that hyperglycemia was produced in all subjects tested. The difference between the means is not statistically significant.

It therefore appears that the sulfonylureas in therapeutic dosage do not inhibit the hyperglycemic response to this dosage of glucagon.

c. Epinephrine differs from glucagon insofar as it reactivates muscle phosphorylase as well as liver phosphorylase.[15] If sulfonylureas exerted their action by interfering with enzymatic hydrolysis of muscle glycogen, then a lessened hyperglycemic response would be seen following epinephrine administration. Lactic acid production would diminish and glucose resynthesis in liver would fall. To investigate this, 0.01 ml. of aqueous epinephrine, 1:1000 solution, per kilogram of body weight, was injected subcutaneously. Blood sugar levels were determined at zero time, 15 minutes, 25 minutes, 35 minutes, and 65 minutes.

*Kindly supplied by Dr. W. R. Kirtley, Eli Lilly and Company, Indianapolis, Indiana.

Figure 3c shows that the response to epinephrine was not altered by sulfonylurea administration under the experimental conditions described. The difference of the means is not statistically significant.

d. Insulin treated diabetics retain tracer insulin-I^{131}* intravascularly longer than do patients who have never been treated with the hormone. This phenomenon has been attributed to antigen-antibody complexing in response to exogenous heterospecies insulins.[16, 17] To see if a correlation existed between insulin retention in the plasma and therapeutic response to sulfonylureas, we applied a technic previously reported from this laboratory.[16] Briefly, a tracer amount of insulin-I^{131} was administered intravenously and a one-hour plasma sample was analyzed for trichloracetic acid (TCA) precipitable and TCA soluble radioactivity. By this means we could detect the per cent of intact insulin and of degraded hormone remaining.[18] Figure 4a shows that no correlation useful for predicting success in treatment was found.

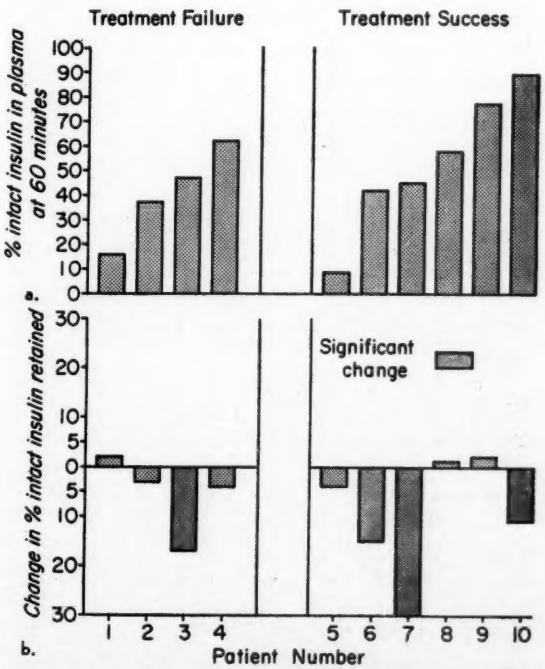

FIG. 4. (a) There is no correlation between plasma binding of insulin-I^{131} and successful treatment with sulfonylureas. (b) Analysis of the relation of the change in plasma binding of insulin-I^{131} and success in therapy shows no consistent correlation.

*Purchased from Abbott Laboratories, Oak Ridge, Tennessee.

A significant change in retention of intact insulin with therapy might reflect alteration of the existing antigen-antibody complexing, or more centrally located processes involved in insulin metabolism. Figure 4b illustrates that changes did occur after sulfonylurea therapy in both success and failure groups. Differences of 5 per cent or less must be considered within the limits of procedural error. Eliminating these from consideration, none of the patients had an increased retention of insulin in one hour. Fifty per cent of successfully treated subjects demonstrated a more rapid disappearance rate of insulin after therapy. A single subject in the treatment failure group showed this phenomenon.

DISCUSSIONS AND CONCLUSIONS

The presence of certain factors favors successful antidiabetic therapy with 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide) and 1-butyl-3-p-toluenesulfonylurea (tolbutamide). Diabetic individuals of either sex who have met the following criteria tend to show a good response: (1) developed the disease after age forty, (2) have had known diabetes for less than five years, (3) have received insulin therapy for less than one year, (4) require less than 30 units of insulin daily, (5) are endomorphic, and (6) do not have severe complications. Approximately 60 per cent of such patients respond favorably. These observations are in accord with reports of other investigators.[12, 13, 19] It is obvious that all of the above criteria need not be present, as some patients responded well who required 50 units of insulin daily and/or had been diabetic for longer than ten years. Carbutamide and tolbutamide seem equally effective and are used interchangeably in many subjects.

Figure 5 presents the response of a newly discovered diabetic male to carbutamide (BZ-55) therapy. After brief initial treatment with insulin, oral medication was substituted with striking success. On day 22, an emergency appendectomy prompted cessation of sulfonylurea therapy. No exogenous hypoglycemic substance was necessary to control glycosuria until 72 hours later, when carbutamide was resumed. Excellent control was maintained until day 80 (not shown) of his course when an elective herniorrhaphy was performed and carbutamide therapy was discontinued. The patient demonstrated the identical time relapse rate as previously. Resumption of the medication resulted in good metabolic compensation. This relapse relation had been observed in another patient and suggests that it may be a reflection of the excretion rate of the compound. Bertram[12, 19] reported that many patients were able to

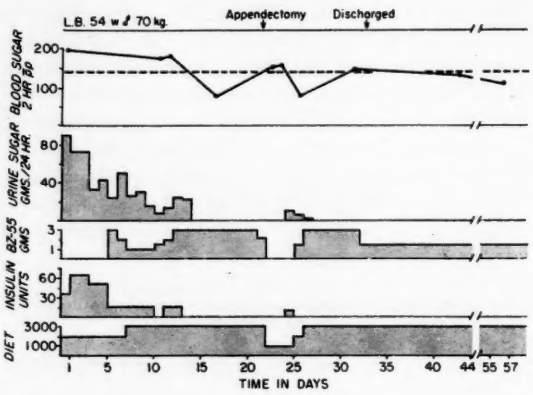

FIG. 5. The response of a newly discovered diabetic to treatment with carbutamide (BZ-55), showing a three-day relapse period following cessation of therapy.

maintain metabolic balance for three to four weeks following a 10 to 14 day course of carbutamide. Four of our patients have been able to discontinue therapy for from four to five weeks without significant intensification of the disease. All eventually relapsed and are now on continuous treatment. An attractive hypothesis to explain these observations is that sulfonylurea therapy diminished insulin need, thereby resting the pancreatic beta cells, with a consequent temporary increase in their ability to supply endogenous insulin, thus allowing transient improvement in the metabolic state. No direct evidence in support of this hypothesis can be offered at this time. The observations may only mean that these specially managed patients were maintaining more strict dietary control during this period. Whatever the explanation, it seems reasonable to prescribe continuous therapy rather than to use a standardized "course" method of treatment as advocated by Bertram.[12, 19]

None of the fourteen patients with the onset of diabetes before age thirty responded. This group included a nine-year old boy with recently discovered disease who required only 10 units of modified insulin daily. Further, the insulin requirement was not appreciably lowered in any of these younger patients. These subjects are of special interest as they represent the ultimate in true pancreatic diabetes and in fact have little or no circulating or pancreatic insulin.[20, 21] We were privileged to study a twenty-seven-year-old male with diabetes consequent to a total pancreatectomy for multiple insulinomata. Frank pancreatic insufficiency was present requiring enzyme and vitamin supplementation. Figure 6 illustrates his hospital course. Carbutamide was completely ineffective in spite of a free

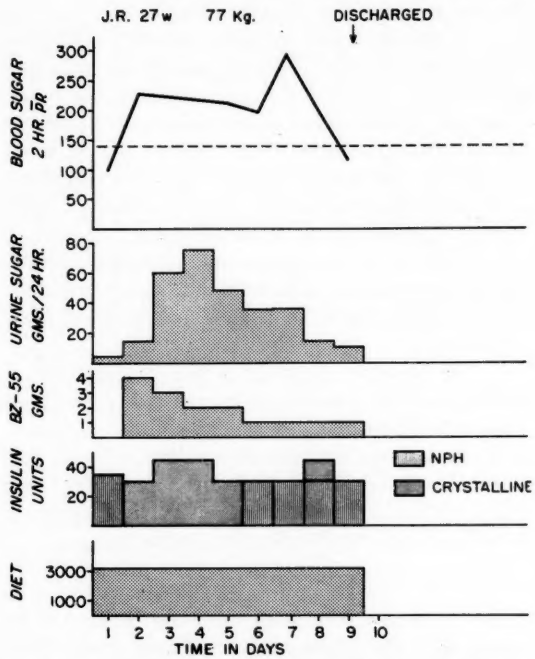

FIG. 6. The response of a totally pancreatectomized male subject to treatment with carbutamide (BZ-55). Sulfonylurea was without effect in controlling diabetes, and it did not increase the effectiveness of insulin.

blood sulfonamide level of 27 mg. per 100 cc. on day 3 of treatment.* Of more importance, his insulin requirement while receiving carbutamide increased out of proportion to that expected from hospital inactivity alone. These observations confirm those of the German investigators[10, 11, 12, 13, 19] and re-emphasize their claims, that for successful hypoglycemic action of these compounds, a functioning, presumably insulin-producing pancreas must be present. Perhaps case selection could be done best by plasma insulin assay.[20] Unfortunately, this technic is impractical as yet.

None of our patients was severely acidotic, although several demonstrated ketonuria. All previous investigators[12, 13, 19] agree that sulfonamide therapy is not as effective in situations of severe stress or in acidosis. We accept this conclusion and consider such situations as probable contraindications for sulfonamide therapy.

The lack of toxicity in our series was encouraging. Before complete assurance can be obtained, long-term controlled therapy must be evaluated. The experiences of Rich,[22] with experimental production of tissue hypersensitivity reactions with the sulfonamides, in addition to the extensive clinical experience in this regard, demand serious consideration and watchfulness. Despite this reservation we feel that these substances can be used in most patients. Subjects with previous sulfonamide hypersensitivity, frank or suggestive collagen disease, or strong allergic histories, probably should be excluded. The gastrointestinal side effects attributable to sulfonylurea ingestion were probably due to direct irritation of the gastric mucosa. Giddiness, drowsiness, increase in tremor, and paresthesias were most likely related to a central nervous system effect, as animal experimentation has revealed such effects unrelated to hypoglycemia when large doses were administered.[23]

In evaluating the metabolic studies accomplished, we were unable to demonstrate that sulfonylurea, in therapeutic dosage, altered either insulin tolerance or the metabolic response to glucagon or epinephrine, suggesting that these agents act independently of insulin or glycogenolytic enzyme systems. Although Mirsky[24] and Williams[25] have shown that under certain conditions sulfonylureas inhibit insulin degradation, our preliminary observations with insulin tolerance tests failed to reveal such an effect.

The percentage retention of insulin-I^{131} in the plasma at sixty minutes shows no correlation with therapeutic response, nor can the change in retention after therapy be correlated definitely with success or failure in treatment. The degree of retention of tracer insulin-I^{131} in the plasma represents the summation of the following factors: (1) quantitative protein binding, (2) degree and rate of destruction of insulin, and (3) hormonal contra-insulin factors. Inasmuch as only 50 per cent of successfully treated subjects demonstrated a significant decrease in the amount of tracer insulin present in the plasma, the most conceivable explanation, if any, would be that the existing antigen-(insulin)-antibody complex had been altered in some fashion. Whether this was due to sulfonylurea or simply a reflection of time alterations cannot be stated. If these compounds act by inhibiting "insulinase" or in some way suppressing hormonal contra-insulin effect, one would expect to see a more consistent response. No valid information can be obtained by studying the trichloracetic acid soluble fraction of radioactivity in the plasma as this involves the metabolism of I^{131} per se, and a given level depends in great part on the thyroid and other tissue uptake and trapping, and on urinary excretion, and is not a static thing even in a given patient. Nevertheless, these data were analyzed, but no correlation of the amount of degraded insulin and

*Blood sulfonamide levels of 10-12 mg. per cent usually are adequate for therapeutic response.

treatment response could be obtained.

More intensive studies of the actions of the sulfonamides in producing hypoglycemia are reported in a separate communication.[26]

SUMMARY

1. 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide) and 1-butyl-3-p-toluenesulfonylurea (tolbutamide) have been used in the treatment of fifty-six diabetic patients. Fifty per cent of the subjects were able to maintain adequate control of their disease without supplementary insulin.

2. Those patients for whom good responses can be predicted are over forty years of age, endomorphic, have insulin requirements of less than 30 units daily, have had diabetes for less than five years, have received insulin for less than one year, and do not have severe diabetic complications.

3. Indications for therapy include essentially all diabetic patients of the maturity-onset type who do not have historical evidence of sulfonamide sensitivity, suggestion of collagen disease, or severe allergic responses of other types. Patients in acidosis and those subjected to severe stress should be given insulin either alone or with the sulfonamide.

4. Serious toxicity was not observed. Nausea, giddiness, drowsiness, and paresthesias appeared as isolated events in a few patients at the onset of therapy.

5. The metabolic response to insulin, glucagon, and epinephrine was not found to be altered in the presence of therapeutic dosage levels of sulfonylureas.

6. Insulin-I^{131} plasma binding (per cent of tracer dose remaining in the plasma one hour after injection) is not consistently altered by sulfonylureas in therapeutic amounts.

SUMMARIO IN INTERLINGUA

Sulfonylureas e Diabete Mellite: I. Evalutation Clinic

1. Esseva usate 1-butyl-3-p-aminobenzenesulfonylurea (carbutamido) e 1-butyl-3-p-toluenesulfonylurea (tolbutamido) in le tractamento de cinquanta-sex diabeticos. Cinquanta pro cento del subjectos poteva mantener un adequate grado de dominio de lor morbo sin insulina supplementari.

2. Le categoria de patientes pro qui on pote predicer bon responsas al therapia con sulfonylureas satisface le sequente criterios: Illes ha plus que quaranta annos de etate; illes es endomorphic; illes ha requirimentos de insulina de minus que 30 unitates per die; lor diabete ha un duration de minus que cinque annos; illes ha recipite insulina durante periodos de minus que un anno; e illes non ha sever complicationes diabetic.

3. Le therapia a sulfonylureas es indicate pro practicamente omne patientes de diabete qui representa le typo a declaration del morbo al etate matur e qui non ha un historia de sensibilitate a sulfonamido, nulle indicio de morbo collagenic, e nulle sever responsas allergic de altere generes. Patientes in acidose e patientes exponite a sever grados de stress deberea reciper insulina sol o insulina in conjunction con le sulfonamidos.

4. Nulle serie toxicitate esseva observate. Nausea, vertigine, somnolentia, e paresthesias se manifestava como evenimentos isolate in un numero de patientes al initio del therapia.

5. Le responsas metabolic a insulina, glucagon, e epinephrina non se monstrava alterate in le presentia de dosages therapeutic del sulfonylureas.

6. Le ligation plasmatic de insulina a I^{131} (i.e. le procentage de un dose traciator remanente in le plasma un hora post le injection) non es alterate uniformemente per le sulfonylureas in quantitates therapeutic.

ACKNOWLEDGMENTS

The authors wish to thank Dr. James Telfer and his associates of the Medical Service, United States Public Health Service Hospital, Seattle, for performing certain of the metabolic studies and allowing us to incorporate their data into this report. We are indebted to Dr. Robert H. Barnes, Dr. Thomas B. Smart, Dr. Sidney Weinstein, and Dr. William Kelly for contributing patient data to this study. We are especially grateful to Miss Maureen O'Connell for invaluable technical assistance.

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Overweight and Obesity

Gross body weight can contribute directly to injury and death in accidents involving motion of the body. The damaging force in a fall is increased with increasing body weight. Moreover, a heavy body is an impediment in avoiding many accidents because it is harder to move or change its direction of movement rapidly. It is not surprising that the insurance companies find overweight people have an excessive mortality rate from accidents.

Nevertheless, there can be little doubt that the major importance of overweight is its association with obesity. Obesity means excessive fatness and it is essential to adhere to the classical definition if confusion is to be avoided.[1, 2] The modern ease and popularity of weighing the body is a mixed blessing. The middle-aged person who is 30, 40, or more pounds heavier than the average for his height is almost inevitably overfat as well. But at lesser departures from the average the relationship between relative body weight and relative obesity is far less reliable, particularly in younger adults.[3] That athletes are often overweight but underfat is well known.[4] Differentiation between gross weight and fatness in men discloses differences in circulatory characteristics pertinent to cardiac performance and health.[5] In many physiological respects the man who is overweight simply because he is fat is at the opposite pole from the man who is equally overweight because of a large muscle mass in his body. The emotional and psychological differences between these types are no less great and may be of greater social significance.

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Sulfonylureas and Diabetes Mellitus:

II. Preliminary Studies of the Mechanism of Action

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Seattle

Effective control of diabetes mellitus in greater than 50 per cent of patients can be achieved with the oral administration of certain sulfonamides.[1, 2, 3, 4] Following the report of Janbon and others,[5] that p-aminosulfonamidoisopropylthiadiazole produced hypoglycemia in man and rabbits, Loubatieres[6, 7, 8] investigated the subject and suggested that this substance stimulated insulin secretion.

Holt[9] concluded that the compound acted by decreasing glucagon secretion because he observed that pathologic changes occurred in pancreatic alpha cells in treated animals and that administration of this compound ameliorated alloxan diabetes in rabbits. Achelis and others,[10] and Franke and others,[11] observed similar pancreatic morphopathologic changes in rabbits and in one human treated with 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide). On the other hand, Chen[12] and Mirsky[13] found a complete lack of effectiveness of sulfonamide derivatives in alloxan diabetic animals which argues against Holt's hypothesis.

Mirsky[14] and Williams[15] have reported that carbutamide and 1-butyl-3-p-toluenesulfonylurea (tolbutamide) delay the destruction of insulin by inhibiting certain enzyme systems. Consequently, these compounds might be expected to diminish the enzymatic degradation of endogenous insulin and to ameliorate diabetes in certain patients.

Loubatieres,[6] Miller and Dulin,[16] and Tyberghein, Halsey and Williams[17] have observed that liver glycogen does not decrease in fasted hypoglycemic animals treated with a sulfonylurea. However, if similar animals were fed glucose, no alteration in liver glycogen occurred even though hypoglycemia was produced. Moorhouse and Kark[18] found no alterations in serum lactate or pyruvate levels in humans treated with these new agents. Also, whereas continuous glucose gavage abolished the hypoglycemic effect, fructose feeding would not do this. Tyberghein and others,[17] demonstrated a decrease in glucose-6-phosphatase activity in livers of sulfonylurea treated rats. These observations show that, at least under certain conditions, the compound decreases hepatic glucose release.

This report is concerned with studies of the general and specific toxicity of sulfonylureas as judged by the growth of young rats and the histologic appearance of their pancreas, liver, and kidneys. It also considers the effect of sodium tolbutamide on the hypoglycemic response in rats previously subjected to hypophysectomy, nephrectomy, adrenalectomy, pancreatectomy, or hepatectomy; investigations of the metabolism of insulin-I^{131} in these animals are included.

MATERIALS

Carbutamide* and tolbutamide,† and sodium tolbutamide,† were administered under standard experimental conditions to locally bred Sprague-Dawley rats. The insulin-I^{131}‡ had characteristics like those previously reported from this laboratory.[19]

METHODS AND RESULTS

A. Effect on Growth

1. *Method.* Thirty-five-day-old rats were segregated into three groups of four animals each and maintained in individual cages for twenty-seven days. One group received finely ground Purina Fox Chow only, another, carbutamide as a 1 per cent drug-food mixture, and the third, a comparable mixture of tolbutamide. The

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*Kindly supplied by Dr. W. R. Kirtley, Eli Lilly and Company, Indianapolis, Indiana.

†Kindly supplied by Dr. C. J. O'Donovan, Upjohn Co., Kalamazoo, Michigan.

‡Purchased from Abbott Laboratories, Oak Ridge, Tennessee.

drug dosage was calculated to provide 800 mg. per kg. of body weight per day. The animals and food containers were weighed initially and at each subsequent feeding. Determinations of the glucose concentration of tail vein blood were performed by the Nelson technic[20] prior to therapy and after treatment for four days.

2. *Results.* Figure 1 depicts the corrected growth curves for the three groups and reveals that hypoglycemic amounts of sulfonylureas do not interfere with normal growth of young rats. The animals appeared well during the test period. This indicated that the multiple processes involved in growth were not affected by these substances.

B. Effect on Organ Weight and Morphology

1. *Method.* The young rats which had been treated with sulfonylureas were sacrificed by aortic exsanguination. Autopsy demonstrated no gross abnormalities. The liver, kidneys, adrenals, and thyroid were weighed. Hematoxylin and eosin stains of sections of the liver and kidneys were made. The pancreas was fixed in Bouin's solution and subsequently processed, sectioned, and stained with chrome-alum-hematoxylin-phloxine by the Gomori method.[21]

2. *Results.* Table 1 shows that there was an increase in mean adrenal and thyroid weights in the experimental group. Although others[11, 16] have made similar observations, these changes are not statistically significant. Hepatic and renal histology was unaltered. A very careful search failed to reveal pancreatic islet cell changes in contrast to the findings of the German investigators.

TABLE 1
Effect of sulfonylureas on organ weight*

Group	Animals	Body Weight	Thyroid	Adrenal	Liver	Kidney
Control	4	152	.008	.025	4.87	.94
Carbutamide	4	124	.01	.027	5.2	1.01
Tolbutamide	4	134	.009	.029	4.5	.96

*All organ weights are corrected for body weight. Correct weight = organ weight/body weight x 100. Although mean increases in thyroid and adrenal weights (in grams) are apparent, these are not statistically significant: thyroid ($p > 0.2$); adrenal ($p > 0.5$). No deviation in liver or kidney weights from controls was noted.

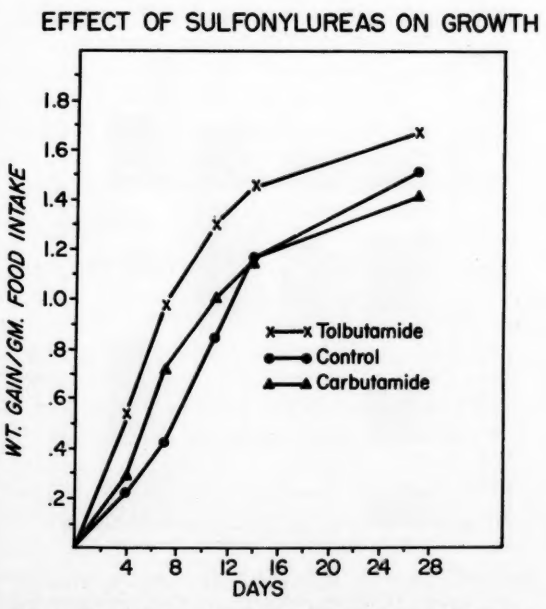

FIG. 1. No alteration of growth and maturation was observed in weanling rats treated with the sulfonylureas for twenty-seven days.

C. Effect on Hypoglycemia under Differing Metabolic Conditions

1. *Method.* Adult female rats weighing about 200 gm. were fasted for seventeen hours with free access to tap water and then gavaged with 2.0 ml. of 10 per cent glucose in water. One hour and fifty minutes after this procedure, 7.2 mg. of sodium pentobarbital was administered intraperitoneally. Two hours after gavage an initial tail venous sample was obtained and the blood processed immediately by the Nelson technic[20] for blood glucose. Sodium tolbutamide was then injected by tail vein over a fifteen second interval. The dosage was constant in all experiments: 350 mg. of drug per kilogram of body weight, dissolved in 0.9 per cent saline, in a total volume of 0.5 ml. One hour later the animal was sacrificed by inferior vena caval exsanguination and the glucose level of this sample determined. Controls received similar treatment except that they were injected with a like volume of 0.9 per cent saline. Each group was composed of at least five animals.

Intact, nephrectomized, adrenalectomized, hypophysectomized, pancreatectomized, and hepatectomized-gastroenterectomized animals were studied. Except for hypophysectomy and adrenalectomy, the operations were performed just prior to the initial blood glucose sampling. Adrenalectomy was performed two hours before the experiment to allow for inactivation and/or excretion of circulating adrenal hormones. Hypophysectomized rats were purchased,* and completeness of the operation was judged by retardation of growth. Nephrectomy was performed by ligation of the renal pedicles close to the

*Purchased from Endocrine Laboratories, Madison, Wisconsin.

pelvis. Pancreatectomy was accomplished "physiologically" by ligation of the duodenal loop, but the hepatic artery and portal vein were not included in the ligature. Hepatectomy-gastroenterectomy also was "physiologic" with ligation of the portal triad and the vessels of the mesenteric root so as to exclude the liver, pancreas, and gastrointestinal tract from the circulation. This technic has been reported previously from this laboratory.[22] Suitable operative controls were performed in each case.

2. *Results.* Figure 2 shows the results of these experiments, with the solid bars indicating the mean net percentage change in blood glucose level from the initial value. Intact rats demonstrated a 28 per cent fall in one hour. Nephrectomy did not alter the response, whereas adrenalectomy permitted a marked increase in hypoglycemic effectiveness. Hypophysectomized rats seemed no more sensitive to the compounds than intact animals. The pancreatectomized rats responded with a slight increase in blood glucose level, but when the decrease in the controls is considered a marked net increase then occurred. Hepatectomized-gastroenterectomized rats had a percentage fall, similar to the intact preparations.

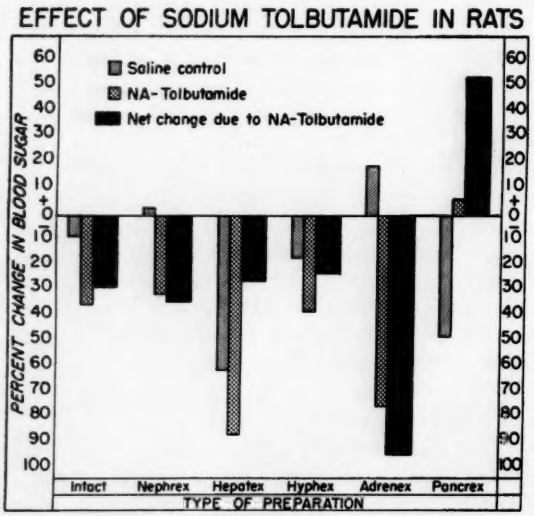

FIG. 2. The net percentage change in blood glucose is unaltered in nephrectomized, hypophysectomized, and hepatectomized rats as compared to the intact animal. Adrenalectomy increases the hypoglycemic effect, whereas pancreatectomy produces a net percentage increase in blood sugar.

D. *Effect on Insulin-I^{131} Metabolism under Differing Metabolic Conditions*

1. *Method.* Insulin-I^{131} (5-10 *uc*) was injected by tail vein fifteen minutes prior to sacrifice into adult female rats weighing about 200 gm. that had been treated as described in the previous section. Insulin dosage was constant in each experiment and averaged 0.004 mg. for the entire series. Intact, nephrectomized, hypophysectomized, and hepatectomized-gastroenterectomized rats were studied. After sacrifice, tissues were removed and processed by the methods previously described from this laboratory.[22] Trichloracetic acid (TCA) precipitable radioactivity was considered to indicate intact insulin, whereas TCA soluble material was taken to represent degradation products of insulin-I^{131}.[23] In order to correct for variations in animal size, the concentration of insulin-I^{131} in each tissue was divided by the concentration in the total body. The resultant ratio expression [T]/[B] was used to indicate the amount of intact insulin in each tissue assayed. The percentage of TCA soluble material present in a given tissue was considered as an index of the amount of degradation.[19]

2. *Results.* Figure 3 illustrates the effect of sodium tolbutamide on the distribution of intact insulin in the preparations studied. Table 2 shows the effect on degradation expressed as percentage of TCA soluble radioactivity in the tissues. There was no effect on the tissue

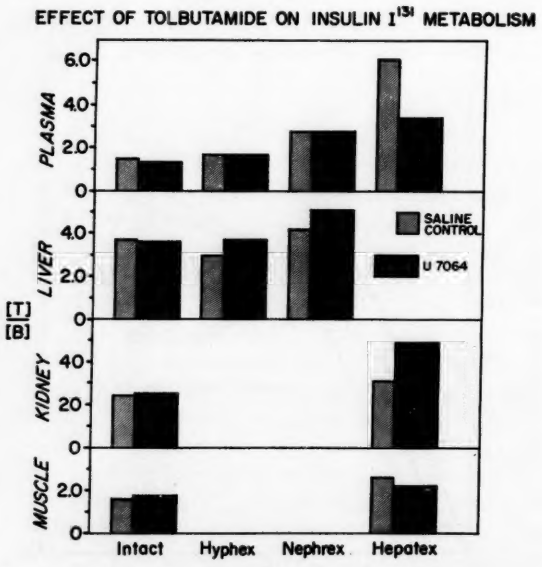

FIG. 3. No effect was observed on the relative tissue concentration, [T]/[B] of insulin-I^{131} in intact, nephrectomized and hypophysectomized rats. An increased concentration of insulin was noted in the kidneys of hepatectomized animals treated with tolbutamide (U7064).

concentration of insulin-I^{131} in the intact, nephrectomized, or hypophysectomized rat. Likewise, no significant difference in degradation could be detected in these preparations. The hepatectomized-gastroenterectomized animals concentrated a greater amount of insulin in the kidney in the presence of tolbutamide, and less insulin-I^{131} was degraded. The plasma levels reflected this apparent trapping. Muscle concentrations were unaffected.

THE EFFECT OF SODIUM TOLBUTAMIDE ON INSULIN I^{131} DEGRADATION

	INTACT		HEPATEX		NEPHREX		HYPHEX	
	Saline	U7064	Saline	U7064	Saline	U7064	Saline	U7064
PLASMA	37	40	13.7	25.0	38	32	47	37
LIVER	35	36			38	33	44	40
KIDNEY	15	12	15.9	7.0				
MUSCLE	36	37	21.8	27.8				

TABLE 2

The figures represent the percentage of total radioactivity in each tissue which is trichloracetic acid soluble. As such, they represent the amount of degraded insulin-I^{131} present. Tolbutamide (U7064) did not affect insulin-I^{131} degradation except in the hepatectomized rats.

DISCUSSION AND CONCLUSIONS

Sulfonylureas alter neither growth rate nor the histologic appearance of the kidneys or liver in young rats. This is reassuring and indicates that they produce hypoglycemia by means other than pituitary growth hormonal suppression or direct hepatotoxicity.

The lack of morphopathologic change in pancreatic alpha cells adds supporting evidence to the finding of Tyberghein and others,[24] that serum glycogenolytic activity (probably glucagon activity) is unaltered in animals treated with tolbutamide. These two observations and the findings of others[13] that sulfonylureas are ineffective in severely alloxanized animals makes the pancreatic alpha cell toxicity hypothesis of sulfonylurea hypoglycemia seem unlikely.

Neither the kidneys nor the adrenals are necessary for the hypoglycemic effect of tolbutamide. Adrenalectomy increases the net effect, probably due to a lack of cortical and medullary contra-insulin and hyperglycemic-homeostatic response. It is not apparent from our data why the hypophysectomized rats had a greater blood glucose fall. The animals were operated on about two weeks prior to use and should have been hormonally deficient. In any event, the experiments illustrate that the compounds do not act by pituitary suppression.

"Physiologically" pancreatectomized animals did not respond with hypoglycemia to the administration of tolbutamide and, in fact, a net percentage glucose increase was noted. In this experiment the standard deviations of the control and treated groups were such as to make the actual difference between the means not statistically significant, and a conclusion that pancreatectomized rats respond with hyperglycemia to tolbutamide is unwarranted until further studies are performed on a more suitable experimental animal. Cox and others[4] found no effect in a totally pancreatectomized human subject which is in agreement with previous investigations.[6, 9]

It was curious that intravenous tolbutamide produced a blood glucose fall in acutely hepatectomized-gastroenterectomized rats. This argues against the concept of Loubatieres that sulfonamide derivatives act solely by stimulating insulin secretion. If this were so, no effect should be observed in such rats. Two possible explanations for the response can be advanced: (1) by removing the major source of insulin degrading enzyme (liver), the endogenous insulin is more effective in the presence of tolbutamide because of increased quantitative substrate competition for enzyme present in other tissues, or (2) sulfonylureas exert a peripheral effect either by augmenting the action of insulin, or independent of it. In support of the first consideration are the demonstrations of Williams[15] and Mirsky[14] that tolbutamide inhibits insulin degradation by liver enzymes. Insufficient information is available to conclude whether or not the sulfonylureas directly affect peripheral glucose metabolism. However, it is of interest that Moorhouse and Kark[18] showed that serum lactic acid levels do not increase in humans given hypoglycemic doses of tolbutamide.

If inhibition of insulin degrading enzyme systems played a significant role in sulfonylurea hypoglycemia, then a lesser amount of degraded insulin should be seen in the tissues of intact rats given a tracer amount of insulin-I^{131} in the presence of hypoglycemic amounts of tolbutamide. As no significant differences could be detected in plasma, liver, kidneys, or muscle in such animals, this raises doubts as to the importance of the previously cited observations[14, 15] that sulfonylureas are inhibitors of insulin degradation. The special circumstances of nephrectomy and hypophysectomy did not alter the distribution and degradation of insulin-I^{131} in tolbutamide-treated rats as compared to their own controls, just as they did not change the hypoglycemic response to the compound. Hepatectomized-gastrointestinally eviscerated rats that received tolbutamide concentrated an increased amount of presumably intact

insulin in their kidneys. Only a small percentage of the total radioactivity was trichloracetic acid soluble indicating but slight degradation. On the other hand, plasma insulin was decreased with a greater amount of degraded material present. If tolbutamide acts as a nephrotoxin in this special instance, it may be that insulin is, in effect, "trapped" in the kidney, with reabsorption of only cleaved fragments and free I^{131}, which would explain why this fraction of radioactivity is increased in plasma and decreased in kidney in comparison to the controls. The slight increase in degraded material present in muscle may also reflect this. Further interpretation of this observation is not justified at this time, but we emphasize the finding because it may indicate a specific action in the proximal convoluted tubule where insulin is concentrated in the kidney.[19]

The sulfonylureas exert multiple effects on carbohydrate metabolism. Further investigations are needed to evaluate the relative importance of the involved mechanisms.

SUMMARY

1. Immature rats were treated for twenty-seven days with 1-butyl-3-p-aminobenzenesulfonylurea (carbutamide) and 1-butyl-3-p-toluenesulfonylurea (tolbutamide) without untoward effect. No alterations were observed in the rate of growth of the animals nor in the structure of the liver or kidneys.

2. Rat pancreatic alpha cellular structure remained intact following prolonged, intensive therapy with carbutamide and tolbutamide.

3. Equal hypoglycemic effect was produced by tolbutamide in intact, nephrectomized, hypophysectomized, and hepatectomized rats. Adrenalectomy increased tolbutamide effectiveness, whereas pancreatectomy abolished it.

4. Insulin-I^{131} tissue distribution and degradation was unchanged by tolbutamide administration in intact rats, whereas hepatectomized preparations concentrated an increased amount of hormone in the kidney as compared to similarly operated controls.

5. These preliminary studies emphasize that although isolated actions of sulfonamide derivatives can be demonstrated, no one action alone can adequately explain their antidiabetic effect in man and animals.

SUMMARIO IN INTERLINGUA

Sulfonylureas e Diabete Mellite

II. Studios Preliminari del Mechanismo del Action

1. Rattos immatur esseva tractate, durante vinti-septe dies, con 1-butyl-3-p-aminobenzenesulfonylurea (carbutamido) e 1-butyl-3-p-toluenesulfonylurea (tolbutamido). Le curso habeva nulle effecto adverse. Nulle alterationes esseva notate in le crescentia del animales, ni in le structura hepatic o renal.

2. Le structura del cellulas alpha pancreatic del rattos remaneva intacte post prolongate, intense therapias con carbutamido e tolbutamido.

3. Le mesme effectos hypoglycemic resultava del administration de tolbutamido in rattos intacte, nephrectomisate, hypophysectomisate, e hepatectomisate. Adrenalectomia augmentava le efficacia de tolbutamido. Pancreatectomia aboliva lo.

4. Le histodistribution e le degradation de insulina a I^{131} non esseva alterate per le administration de tolbutamido in rattos intacte. In rattos hepatectomisate, le concentration renal del hormon esseva augmentate per tolbutamido.

5. Iste studios preliminari indica que isolate actiones de derivatos sulfonamidic es demonstrabile sed que nulle tal action per se suffice a explicar adequatemente le effectos antidiabetic de ille derivatos in homines e animales.

ACKNOWLEDGMENTS

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GROUP DISCUSSION OF THE PRECEDING PAPERS ON THE ORAL ANTIDIABETIC COMPOUNDS

FREDERICK M. ALLEN, M.D., (*New York City*): Preliminary screening confirms essentially what others have found: that BZ-55 makes severe juvenile diabetes no better and sometimes worse; in rare insulin-resistant cases it may radically reduce insulin requirement; it is seldom promising for ordinary cases whose insulin requirement is more than 40 units daily. I have obtained none of the brilliant results which are reported in obese patients, because I prefer treatment by weight reduction. Ambulant therapy being the ultimate requisite, my sustained use of the tablets has been limited to forty-six patients thoroughly dependable and controlled under office treatment. Control here means normal urine, and blood sugar below 150 mg. after the morning and evening meals.

Three patients who had been controlled by diet alone enjoyed extra carbohydrate when on the tablets. Twenty-eight others on BZ-55 who had required 15 to 35 units of insulin daily were controlled without insulin, but several of them had to reduce their carbohydrate somewhat. The oral medication has a decided relation to diet and does not permit indiscriminate eating. The remaining fifteen patients could not discontinue the stated insulin dosage with glycosuria or especially hyperglycemia. Five of these failures were turned into partial successes when Dr. Kirtley and the Lilly Company supplied Ultralente insulin. Though it may not have much longer action than protamine insulin, these five patients were controlled on the tablets daily and this insulin every other day or twice a week.

The fact that these drugs reduce sugar only in the normal or mildly diabetic organism, possessing some native insulin, has suggested the possibility of an insulin-mediated action. A retarded destruction of insulin should be ideally displayed in severe human cases receiving large doses of insulin, but the opposite is true.

Figure 1 shows experiments on rats designed to show the effect of carbutamide upon insulin action. The data show that an increase of dosage of insulin increases the intensity of the effect only slightly but the duration

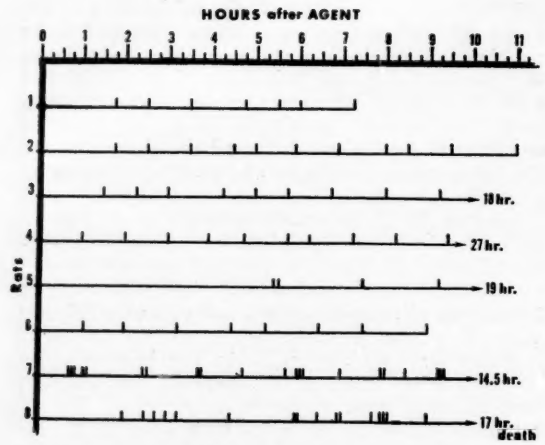

FIG. 1. Control of hypoglycemic convulsions in rats by injection of glucose following the intraperitoneal injection of insulin with or without carbutamide.

Every cross hatch on a line indicates a subcutaneous injection of 0.2 gm. glucose (1 cc. 20% solution). Each line (except No. 5) begins with an intraperitoneal injection of insulin, and hours are measured from it. When too long for the chart, the early portion shown is typical of the whole. The individual lines represent the following: 1. Insulin 20 units; convulsions and required glucose injections continually 7 hours. 2. Insulin 30 units; resulting period of convulsions 11 hours. 3. Insulin 60 units; convulsive effects 18 hours (duration of depressed state following last convulsion increases with the dose). 4. Insulin 100 units; convulsive effect 27 hours. 5. No insulin. Carbutamide 2 gm. per kg. subcutaneously. Extreme weakness and flaccid collapse. Glucose injected when death seemed imminent. (Only four injections in 19 hours). 6. Insulin 20 units. Carbutamide 0.25 gm. per kg. subcutaneously, 3 hours before insulin. The frequency of convulsions is not greatly changed but they are associated with some collapse. The true insulin effect seemed to have about the same duration as in line 1, because the last two attacks were purely collapse, attributable to carbutamide. When convulsions do occur briefly they are explainable by potentiation of residual insulin. 7. Insulin 60 units; carbutamide 1 gm. per kg. subcutaneously 3 hours before insulin. The dangerous collapse crises requiring rapidly repeated glucose injections are totally different from effects of higher insulin dosage. Convulsions and collapse mingled at first; later there was only collapse. The extra glucose required to save life may account for the shorter total duration as compared with 60 units of insulin alone (line 3). 8. Carbutamide 0.5 gm. per kg. 3 hours after 60 units of insulin. Effects similar to preceding, but more prolonged and ending fatally.

very markedly. In rats weighing 250 to 350 gm., fasted 12 to 24 hours, the cross hatches on the lines of the chart represent glucose injections required for control of convulsions which recur at something like hourly intervals for about 7 hours after 20 units of insulin, for 11 hours after 30 units, for 18 hours after 60 units, and for 27 hours after 100 units. These figures can vary widely with different size, individuality and nutritive condition of rats, but the results are uniform in matched animals or in the same animal at different times. It is immaterial whether the insulin is injected subcutaneously, intramuscularly, or intraperitoneally. I have shown that the results do not represent delayed absorption but actually measure the time required for the body to dispose of the main bulk of injected insulin. A milder hyperinsulinism is evidenced by depression persisting for one to several hours after the last convulsion. Also, glucose serves not to neutralize insulin but only to increase the blood sugar. Hence, regardless of the insulin dose, every convulsion is relieved by only 0.2 gm. of glucose subcutaneously.

The different mechanism of carbutamide hypoglycemia from that of insulin is displayed in three ways: (1) Symptoms: While it is said that convulsions are produced in chickens by these drugs but not by any amount of insulin, carbutamide hypoglycemia does not produce convulsions in the rat. Line No. 5 in the chart shows data obtained from a rat that survived 2 gm. per kg. of carbutamide subcutaneously. There was extreme flaccid weakness for nineteen hours, with never any convulsion or spasticity even when death was imminent. The symptoms were relieved by four injections of 0.2 gm. of glucose. (2) When given together with insulin, carbutamide, if it acts by retarding insulin destruction, should behave like an increase of insulin dose. On the contrary, the carbutamide intensifies the hypoglycemia, producing dangerous crises in which life is narrowly saved by rapidly repeated glucose injections. Death may occur with dyspneic convulsions, with intense pulmonary congestion. This suggested the possibility that some animals that are too far gone to be saved by glucose alone may be saved by epinephrine. No such prolonged desperate crises result from any increase of insulin dose from 20 to 60 or 100 or more units; allowing a remarkably short time for absorption, the one trivial glucose injection always ends the convulsion. (3) Another difference is that the duration of effect is not correspondingly lengthened, as it must be by any accession of insulin, either through pancreas stimulation or through retarded destruction. There may be one or two extra convulsions if the persisting mild hyperinsulinism, which was previously mentioned, becomes potentiated. Confusion may be best avoided by selective timing of larger doses, which distinguish between the convulsive action of insulin and the flaccid collapse of carbutamide after the insulin action is ended, as shown in lines 7 and 8 of the chart.

Diabetes is insulin deficiency, generally absolute, some-

times relative. Carbutamide does not contribute insulin either directly or through retarded destruction, but reduces blood sugar by an entirely different mechanism. Therefore, is this therapy physiological or unphysiological? Actions have been suggested through glucagon or other agencies, which may be physiological. Incidentally, I took care to duplicate the foregoing experiments with glucagon-free insulin, kindly furnished by Dr. Kirtley.

Clinically, I view the blood sugar as the most delicate index of a general metabolic disorder. I also insist that a standard of normality need not be arduous for either doctor or patient if both are in earnest. By adhering to it I claim a record of forty years without a diabetic complication in a cooperative patient. I therefore hold that every complication is the fault of either doctor or patient. I am glad to be recorded as the first and most consistent upholder of this absolute doctrine, which is increasingly supported by the trend of statistics showing that the supposed constitutional factor shrinks as control improves. Confusion was formerly created by statistics purporting to show similar outcomes in controlled and uncontrolled cases when no case was actually controlled. The time as well as the kind of complication, or its absence, are determined by variable predisposition. Exceptions may be no more than are found among nondiabetics. I invite confirmation by every doctor who will search his records and verify that complications are regularly preceded by long and important abnormalities of the blood sugar level. Therefore I am unwilling to abandon the standard of normal blood sugar for the mere convenience of oral medication.

Even if the new drugs are not clearly toxic like synthalin, there is the question whether they make a deceptive artificial reduction of blood sugar without correction of the fundamental disorder. Insulin is known to arrest the majority of complications, and if there were opportunity I would test these drugs against other conditions than acidosis, in which they are said to fail. A large clinic should select cases in which the blood sugar can be kept normal by the tablets but not by diet alone, and the influence on existing complications may furnish a decisive lesson.

In the prevailing uncertainty, I make no prolonged use of doses higher than 1 or 1.5 gm. per day, and I limit the cases to those that can maintain normal sugar on this dosage. I hope that these drugs may prove safe and valuable under proper precautions, but the greatest danger will be in departures from physiological control.

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): Through the kindness of Drs. Kirtley and Cox, I have had the opportunity of a preview of their splendidly conceived and executed studies of the sulfonylurea compounds which are of great interest to all of us interested in the welfare of diabetic patients. It is comforting to know that immediate side effects are practically nil.

I would like to ask Dr. Cox or Dr. Kirtley if it is known what are the effects of these compounds on experimentally produced hydropically degenerated islets of Langerhans. It would appear that further stimulation of islets in this state would have an unfavorable effect. This aspect might be of importance in the young diabetic with an acute onset of his diabetes. With the possibility of this unfavorable effect and the fact that clinically it has been shown that the prospect of benefiting the young diabetic with these compounds, is practically nil and it would seem unwise to give them to children at this stage.

Our experience with sixty-five patients would indicate that these compounds control the glycosuria and hyperglycemia in approximately two-thirds of adult patients, most of whom were overweight.

Also, the need for insulin may be greatly reduced in those who are relatively resistant to insulin—taking over 100 units daily—when either carbutamide (BZ-55) or tolbutamide (Orinase) is added to insulin therapy.

We have employed four methods of detecting favorable sensitivity to the sulfonylureas.

1. Having altered therapy if necessary to allow hyperglycemia and glycosuria to occur, quantitative determinations of the sugar in the urine are done for a preliminary five-day control period. The sulfonylurea compound is given—4 gm. daily—for five days and then withdrawn. Significant changes in the degree of glycosuria during these five days in contrast with that found in the preceding and succeeding five days, the diet being constant, will indicate whether or not there is immediate responsiveness to the drug. It is realized that delayed responsiveness may be missed by this method.

2. A profile of sugar concentrations in the blood before and after several days of therapy. Samples of blood are taken before each meal and at bedtime. These observations are made under controlled conditions and with the diet constant throughout.

3. In surveying our Outpatient Clinic, patients were observed for three consecutive periods of two weeks each. Placebo tablets were given in weeks 1 & 2 and in weeks 5 & 6. Either carbutamide or tolbutamide was

given in weeks 3 & 4. Using "Tes-Tape" each patient tested the urine five times daily and brought the used portions of the tape to the clinic each week. The tapes were graded according to color. In this manner it was possible to detect alterations in the frequency of the various concentrations of glucose in the urine.

4. The fourth plan may be completed in six hours without having the patient admitted to the hospital. Adjustments in insulin or diet are made to insure the presence of hyperglycemia and glycosuria at the beginning of the test. A sample of blood is taken at the onset and at the end of six hours. Two grams of the drug are given at the beginning and one-twelfth of the patient's total diet is given in liquid form at two-hour intervals during the test. A significant reduction of the hyperglycemia during the six hours under these conditions indicates a prompt response to the drug. Delayed responses may be missed when this method is used.

We clinicians must rely on the scientists to determine how these preparations reduce the blood sugar and whether the means by which they accomplish this end provide reasonable assurance that we shall have no cause for regret after their prolonged use.

It is clear that most, but not *all,* of the patients who derive apparent benefit from the sulfonylurea compounds are over forty years of age.

The duration of the diabetes has not significantly altered the effectiveness of these drugs in our patients.

Over 80 per cent of middle-aged and older diabetics are overweight when they seek treatment for diabetes. Will the degree of obesity be increased by the elimination of glycosuria by these simply administered drugs? Practically all obese diabetics who have never received insulin may have their diabetes controlled merely by reducing their weight by decreasing the caloric intake. There is a danger that the effectiveness of the new drugs will detract from the attention now given to the benefits of reducing the obese patients. Undernutrition and sulfonylurea therapies appear to supplement each other, hence, it would appear wise to consider them as inseparable for the optimum treatment of overweight diabetic patients. It is realized that many patients who are obese do no lose weight and in such cases a supplementary measure which will control their diabetes is to be commended.

An effective combination of the advantages of judiciously reducing the obese plus the sulfonylurea therapy could mean a new and happier era for the majority of diabetic patients.

If these drugs are released for general use the dangers of sudden withdrawal of insulin from patients who may derive no benefit from them must be recognized.

It would appear that for any patient taking moderate amounts of insulin, a test for effectiveness of the sulfonylurea compounds should precede a major reduction of insulin. This is especially so for patients beginning sulfonylurea therapy on an outpatient basis.

HOWARD F. ROOT, M.D., (*Boston*): I appreciate the privilege of hearing these two reports of new studies concerned with the action of sulfonamide derivatives. Dr. Cox has given reassuring data, again indicating that these drugs do not interfere with growth in young animals and that no evidence was obtained by pathologic studies of damage to kidneys or liver following their use. The evidence which they submit, that an inhibition of insulin degradation may be one of the facts, is also in support of the idea that sulfonamides have more than one effect. Dr. Kirtley also has given much new data indicating the absence of toxic effects. We have then, as the central effect of these drugs, the probability, based upon data already given, that these drugs may act by stimulating the beta cells to release insulin. If it can finally be proved that BZ-55 or other sulfonamides can stimulate the release of insulin, reduce the rate of its degradation or neutralize anti-insulin factors of unknown nature without serious deleterious side effects over a long period, then these substances may truly prove to have a useful place in our treatment of certain older patients with diabetes.

Our own experience at the New England Deaconess Hospital includes the use of BZ-55 in 160 patients and of Orinase in more than 50 patients. The 160 patients who have received BZ-55 include 86 females and 74 males. Only 3 patients were between 14 and 19 years of age, 15 between 20 and 39 years, 67 patients between 40 and 59 years and 74 patients between 60 and 79 years. One patient was 95 years of age. In the group 41 patients have had diabetes less than a year, 72 patients have had diabetes from 1-9 years, 37 patients have had diabetes from 10-19 years and 12 from 20-37 years. In 89 cases previous insulin had been used and in 71 patients insulin had been used for periods varying from a few months to more than thirty years.

We have come to rely upon the four-hour test for the selection of patients who are sensitive to insulin. This test depends upon giving to patients in the fasting state, without having insulin for at least 48 hours, 3.0 gm. of BZ-55 and noting the fall in blood sugar which occurs at the end of four hours. When the blood sugar fell from 20 to 40 per cent, the result was

considered positive and so far, in every patient with such a positive test, the use of BZ-55 has been successful. Toxic skin reactions have been rare. If we omit from these series the patients whose four-hour tests showed them to be insensitive and patients for whom we have not a sufficiently careful follow-up, I may say that among 113 patients treated with BZ-55 there are 15 who have had it for less than two months, but 57 patients have had the substance for periods from 4 to 6 months. Diabetic control has been good in 82 per cent of the series. In general our clinical results are the same as previously reported, again emphasizing the fact that the substitution of BZ-55 or Orinase in young patients of long duration, in complicated cases or in cases with acidosis, has been unsuccessful and may even be dangerous.

RACHMIEL LEVINE, M.D., (*Chicago*): We have used these drugs on patients and experimental animals since the end of November 1955.

We have employed the same kind of test which Dr. Root showed here, namely giving two to three grams of either BZ-55 or Orinase to patients in the morning (without their morning insulin) and estimating blood sugar levels for four to six hours.

In normal individuals the fall of blood sugar from control values is about 20 per cent. In the adult responsive diabetics, the fall in blood sugar is in the 40 to 50 per cent range. However, in the juvenile group there was either no effect (as compared to a placebo control) or some rise in the blood sugar.

Chronic studies were done in the Metabolic Unit. In those patients who were responsive to the test dose, chronic therapy was effective in controlling the glycosuria and the hyperglycemia. It didn't seem to matter whether the patients had or had not taken insulin for a long time before.

In the German literature it is stated that the sulfonylureas acted less effectively in patients who had been on insulin therapy for some years prior to the test. We could not confirm this statement.

There was never, as far as we can tell, any potentiation of exogenous insulin. If one allows the juvenile diabetic a sufficient control period for stabilization, one cannot substitute the drugs for any significant amount of insulin.

In normal animals, mainly dogs and rats, given either drug, the blood sugar falls. In depancreatized animals, we could not get any potentiation of insulin action. In acutely depancreatized animals the developing hyperglycemia was not influenced by injection of BZ-55. In eviscerated dogs sugar utilization is not increased by BZ-55.

Using I^{131}-labeled insulin and determining its rate of disappearance from plasma, it can be shown that BZ-55 had no effect on that rate, i.e., presumably on the rate of tissue uptake of insulin.

I should like to emphasize one point, arising out of the possible mechanism of action. This may be potentially of great importance and practical significance in the use of these drugs over a long period of time in patients.

If the view, expressed first by Loubatieres in 1944, is correct, that the major action of these drugs is the stimulation of the beta cell to secrete whatever insulin it may have stored, then one ought to ask the question: How long is it possible to continue doing this?

It may be a truly stimulatory action which improves the function of the beta cell. However, it is also possible that it may exert a deleterious, exhausting effect in time.

There remain of course other possibilities (as emphasized by Dr. Cox and Dr. Kirtley) of a multifaceted action of these drugs.

The significance of the depression of glucose-6-phosphatase activity in the liver is doubtful, because it is at variance with the fact that the sulfonamides do not interfere with the action of adrenalin and glucagon in raising the blood sugar. Also they do not exert any hypoglycemic effects in the absence of the pancreas despite the increased glucose-6-phosphatase activity in the livers of such animals.

At this time we should focus our attention on the problem of the pancreatic action of these drugs, to be sure that no dire irreversible effects be initiated by chronic administration.

CHARLES H. BEST, M.D., (*Toronto*): There is very little remaining for the fifth speaker to say. We have been working in this field under the auspices of the Toronto Diabetes Association. The President of that group, Dr. Leibel, is here today, and the next issue of the *Canadian Medical Journal* will record the preliminary findings of the Toronto clinicians and experimentalists.

These findings are essentially the same as those which you have heard from others. I find a considerable and widespread confusion between the results of acute experiments and of the more prolonged ones. This applies to the literature and to our discussions here.

It is interesting that some clinicians believe that they can predict from a short-term study of blood sugar what the long-term response of a patient is going to be. I expect that there will be some disconcerting exceptions to these findings.

The evidence for the stimulation of the pancreas by the sulfonamides is accumulating as some of the previous speakers have said. Loubatieres who works in the famous University of Montpellier (where Hédon did cross-circulation experiments in the early part of this century, and obtained some evidence indicating the presence of the internal secretion of pancreas) has conducted experiments which indicate liberation of insulin from the pancreas of the sulfonamide-treated dog. This insulin is carried by the "cross circulation" to a depancreatized dog whose blood sugar is lowered. Dr. Houssay in South America has confirmed these findings.

Various workers have reported the absence of effect of the sulfonamides on the blood sugar of depancreatized dogs. In our department, Dr. R. E. Haist, who has spent many years studying the effect of continuous injections of various materials on the granules of the beta cells finds an immediate degranulation when BZ-55 is given, (suggesting that there may be quick outpouring of insulin) and a more prolonged stimulating effect which perhaps suggests growth of islet cells, but the other substances which stimulate islet growth have a tendency to raise the blood sugar. The detailed effects of sulfonamides on beta cells remain to be worked out. There is no convincing evidence that inhibition of alpha cell function accounts for a significant part of the hypoglycemic effect of the sulfonamides. Some of the earlier findings suggested that a decrease in thyroid function was an important factor in the antidiabetic action of the sulfonamides but this mechanism does not appear to play a very important role in man.

There is some evidence for an extrapancreatic effect in dogs, the mechanism of which has not yet been elucidated. In one depancreatized dog which Mrs. Anna Sirek has been studying in my laboratory, BZ-55 had only a moderate effect in decreasing the insulin requirement. In another, apparently comparable, depancreatized dog the insulin requirement decreased to the vanishing point. This dog has now in fact been maintained on BZ-55 alone without insulin for many weeks and the blood and urine sugars are essentially normal. This effect is obviously not a potentiation of insulin and it will be extremely important to determine how the sulfonamides do exert their chronic effects in animals which respond in this way.

The decreased glucose-6-phosphatase activity which has been reported after sulfonamide has not been observed in depancreatized animals. This effect may therefore well be associated with insulin administration.

It is obviously much too early to predict what place in the therapy of diabetes the sulfonamides will eventually occupy. They may be replaced by more physiological substances with the same action.

I would remind you, in conclusion, that these sulfonamides are not substitutes for insulin. They may be therapeutically useful; they may be very nearly free of toxic properties, but they are not physiological substances.

THOMAS H. MCGAVACK, M.D., (*New York City*): In view of the continuing need for therapy in a majority of patients with diabetes mellitus, a satisfactory hypoglycemic agent will be used for a long period of time in any given subject. It therefore becomes important, not only to ascertain the nature and degree of the blood and tissue sugar effects, but also the presence of any undesirable actions. In this connection, we have studied thyroid function in thirty-four individuals as measured by I^{131} uptake. When 4 gm. of carbutamide were given daily for four days, the average twenty-four-hour uptake of I^{131} decreased from 28 to 10 per cent. By the same technics, in patients given tolbutamide the decrease was from 29 to 20 per cent.

In longer term studies of patients using one of the hypoglycemic agents continuously in maintenance doses of one or two grams daily, we have determined thyroidal uptake of I^{131} at zero or control time, and after two weeks and nine weeks of therapy, respectively. In these subjects, the administration of carbutamide was associated with an average value of 30 per cent I^{131} within the control period, a 20 per cent value at the end of two weeks and a 14 per cent value at the end of nine weeks. With tolbutamide, the corresponding figures were 21, 18 and 18 per cent respectively.

With the exception of the changes in I^{131} uptake after four days of therapy with four grams of carbutamide daily, none of the figures mentioned above is statistically significant. Nevertheless, they show a trend, particularly in the case of carbutamide, towards an alteration in thyroid function. The widespread acceptance of these agents for long term usage should await more extensive studies in a wide range of dosage and for longer periods of administration.

ERNEST BRUCH, M.D., Ph.D., (*Rockford, Illinois*): We did not get started until February 15 of this year and have studied 23 patients; 17 of these were successfully treated.

We can confirm some of the statements which have been made, namely, that neither the duration of the diabetes nor the insulin requirement can be used to estimate whether or not a given patient will be successful. We have one case where the diabetes had lasted for 22 years, and two cases of 12 years' dura-

tion; all were successful. Two cases which had been impossible to control satisfactorily with 70 to 80 units of insulin, are now getting along well on daily maintenance doses of 1.0 gm. of carbutamide.

The other statement was about the quick sensitivity test to carbutamide. This is very interesting but may not be the complete clinical answer. There is a statement in the German articles that success may be obtained rather late in some cases. If we can afford to wait a while, we still may get those. We give our patients seven days; three or four days to achieve control, and three more days to make sure it holds.

We have been able to confirm furthermore observations on the carry-over effect which have been made here and there, namely, that when it was necessary to discontinue the drug because of toxicity or another reason, the controlling effect on carbohydrate metabolism still ran on for some time. In one of our cases it was ten days, and in another one it was full nineteen days. This is still not sufficiently explained.

I now come to a technical point which I believe is important for all those who start doing carbutamide blood level determinations in their laboratories. Dr. Kirtley mentioned that his carbutamide levels ran between 4 and 17 mg. per cent. We had from 7 to 24 mg. per cent and were wondering whether or not we had made a mistake; but we found the higher levels confirmed in the German literature. It is advisable not to turn over these tests simply to a laboratory technician without having a qualified biochemist to supervise the procedure. The outmoded teaching in older books on sulfonamides and in laboratory handbooks is that one may simply use a sulfanilamide standard and arrive at the blood level of the higher sulfonamide by using a correction factor which is proportional to the molecular weights involved. This theory became untenable when Gantrisin became known (theoretical factor 1.55, actual factor 2.26). There was a beautiful opportunity to check this again when chemically pure carbutamide was made available to us. Dr. S. Natelson assisted with this. While the theoretical factor from sulfanilamide to carbutamide is 1.58, the actual factor came out at an average of 2.06. Therefore, if your laboratory technician looks into the book and wants to work with a sulfanilamide standard and a correction factor, have this first checked against a pure carbutamide solution. After the factor has been reliably determined in this manner, one can proceed from there.

STEFAN S. FAJANS, M.D., (*Ann Arbor, Michigan*): In an attempt to elucidate the mechanism of action of the sulfonylurea compounds extensive metabolic balance studies and numerous individual testing procedures have been performed before, during, and following their administration in the following individuals: normal young men; middle-aged, obese diabetics; unstable diabetics; patients with diabetes mellitus and coexisting Addison's disease, Cushing's syndrome, panhypopituitarism and acromegaly. First of all, we have also demonstrated that the sulfonylurea compounds do not interfere with the hyperglycemic action of adrenalin and glucagon and cause no consistent change in the sensitivity to exogenous insulin. In addition, we have found no direct or consistent effect on balances of nitrogen, sodium or potassium. We have observed no significant change in urinary excretion of 17-hydroxycorticoids, and 17-ketosteroids. There has been no effect on Prednisolone-induced loss of carbohydrate tolerance and no modification in the metabolic effects produced by Prednisolone. In addition to ruling out some of the possible mechanisms of action discussed already, our data indicate that the sulfonylurea compounds do not depress the pituitary-adrenal system and do not antagonize the peripheral effects of adrenal corticoids.

Determination of Serum Insulin by the Rat Diaphragm Method

Further Observations in Diabetic and Nondiabetic Subjects and in Hyperinsulinism

A. F. Willebrands, M.Sc., and J. Groen, M.D.,† Amsterdam, the Netherlands*

In 1952 Groen et al.[1] described a method for the determination of the insulin content of blood serum with the aid of the isolated rat diaphragm. Since our last publication,[2] a few papers of other authors dealing with the same subject have been published. It is the object of this communication to review this work and to describe our further experiences.

Using a technic with a singled hemidiaphragm for each determination, Vallance-Owen and Hurlock[3, 4] confirmed the fundamental observation that normal serum increases the glucose uptake of diaphragm tissue. This increase is inhibited by incubation of the serum with cysteine or glutathione, which makes it probable that it is due to insulin. With their technic these authors calculated the normal fasting level of plasma insulin to be between 3 and 8 x 10^{-5} U/ml. This is much less than the figures reported by Groen et al. One hour after 50 gm. of glucose by mouth they found up to tenfold increases in insulin content of the serum over the fasting level.[3]

Randle[5] likewise demonstrated the effect of normal serum with the aid of the rat diaphragm test and confirmed that this effect diminished or disappeared after treating the serum with cysteine or glutathione. Small amounts of insulin were recovered satisfactorily when added to normal serum. This author found the insulin content of normal human plasma, taken two and a half hours after 50 gm. of glucose by mouth, to be 10-20 x 10^{-3} U/ml. These figures are higher than those given by Vallance-Owen et al. and by Groen et al.[1] for fasting values. The insulin activity of plasma from acromegalic patients was found by Randle to be significantly greater,[6] the activity of plasma obtained from patients with hypopituitarism[7] significantly less than that of normal human plasma. On this evidence the author suggested that the level of growth-hormone might increase or influence the insulin content of the insulin-like activity of human plasma.

These results, which to a great extent confirmed our findings, have encouraged us to use the rat diaphragm method for a more systematic investigation of the insulin content of the blood in health and disease.

METHODOLOGY

The determinations of blood insulin in the present investigation were performed as described previously[1] with the following modifications:

1. In most cases the whole diaphragms of eight rats of 80-100 gm., fasted for twenty-four hours, were divided into five pieces in order to be able to compare two unknown solutions with two insulin solutions of known strength (usually 10^{-4} and 10^{-3} U/ml.). As the sensitivity of the diaphragm for insulin diminishes by dividing the tissue in smaller pieces, the insulin effect (for the same insulin concentration) is smaller with fifth diaphragms than with quarter diaphragms (as used previously). However, the difference is not great and therefore this disadvantage was accepted with the advantage of testing two unknown solutions in one experiment.

In every determination this procedure of pooling the fifth diaphragms of eight rats was repeated five times, so that a statistical calculation of the significance of the results was possible.

2. The pooled fifth diaphragms were weighed prior to the incubation in the glucose buffer serum-mixtures instead of afterwards.

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3. Glucose determinations were carried out with the anthrone method described by Van Munster[8] in the following way: 0.5 ml. of incubation fluid is deproteinized with 5 ml. of 5 per cent trichloroacetic acid. After centrifuging 0.5 ml. of the clear supernatant solution is mixed in a test tube with 10 ml. of a solution of 0.2 per cent anthrone in sulfuric acid of specific gravity 1.72 and then heated in a waterbath at 100° C. for six minutes. After cooling the light absorption of the resulting blue-green solution is measured at 635 mμ, and the observed extinction values compared with the extinction values of known glucose solutions treated in the same way.

4. Serum dilutions in the glucose buffer mixture were always 1 in 5 unless otherwise stated.

5. From the figures obtained for the increase in glucose utilization by the addition of the serum, the insulin concentrations in the serum solutions were calculated in a way similar to that described by Randle.[5]

This author showed that a linear standard curve is obtained when the cube root of the absolute glucose uptake is plotted against the logarithm of the insulin concentration. As can be calculated from the data given by Randle in his publication, a linear regression line is also obtained when the cube root of the insulin effect on the glucose utilization is used instead of the glucose uptake itself. We could confirm this experimentally (figure 1), at least approximately, when working with insulin concentrations ranging from 10^{-4} to 10^{-2} U/ml. of incubation medium.[9]

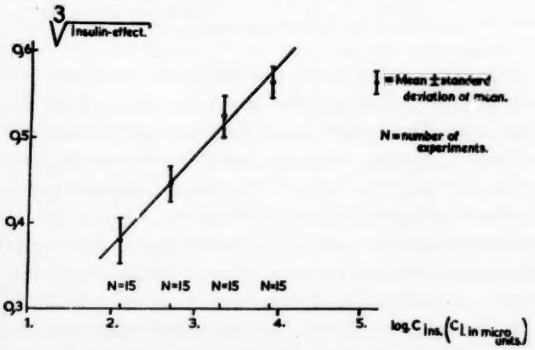

FIG. 1. Regression line showing linear relationship between the logarithm of the insulin concentration (in micro units per ml. of incubation medium) and the cube root of the effect of insulin on glucose utilization (mg. of glucose per 100 mg. of wet tissue).

In every determination the effects obtained with two insulin concentrations of known strength were used to construct a linear regression line in the way outlined above and with the aid of this regression line the insulin content of the serum under investigation was calculated.

SENSITIVITY AND ACCURACY OF THE RAT DIAPHRAGM METHOD

All investigators, who work with the rat diaphragm as a test-preparation for small concentrations of insulin, report that the sensitivity of the preparation can vary to a fairly large extent, even when a rigidly standardized technic is used. The cause of these variations is still unknown.

The lower limit of sensitivity in the test as reported in the literature differs rather from author to author. In recent publications Vallance-Owen et al.[3] report that 10^{-5} U/ml. could still be detected while Randle[5] found that 10^{-4} U/ml. is the lowest concentration of insulin that produces a significant stimulation of glucose uptake. In our former papers, [1, 10] we reported that the lower limit of sensitivity found with the technic described there was often 10^{-5} U/ml., especially when working with hemidiaphragms. Since then, especially when fifth diaphragms are used, the minimum concentration exerting an effect was found to be higher, viz 10^{-4} U/ml.

The variations in the sensitivity of the diaphragm tissue for insulin, from experiment to experiment, make it necessary to run standard insulin solutions together with the solutions to be tested in every experiment.

To give an impression of these variations in sensitivity and also of the reliability of values obtained for the effects of insulin, we have put together in table I the results obtained with two insulin concentrations of known strength (10^{-4} and 10^{-3} U/ml.) in forty-eight experiments. Every experiment consisted of five replicates. The mean value of the effect observed with addition of 10^{-4} U/ml. in such an experiment was designated as a; with 10^{-3} U/ml. as b; the standard deviations respectively as sdp_a and sdp_b; all values expressed as mg. of glucose/100 mg. wet tissue in ninety minutes.

Of these forty-eight experiments eight had to be discarded because a and/or b did not differ significantly from zero or because there was no significant difference between a and b. In one experiment a and b were abnormally high, viz three times the mean value found in the remaining thirty-nine experiments. Of these remaining experiments the mean value of a was 0.076 ± 0.033 and of b more than twice as high, viz 0.175 ± 0.052 mg. of glucose per 100 mg. of rat tissue in ninety minutes. The mean value of the standard deviation sdp_a was 0.036 and of sdp_b 0.051. The

TABLE 1

Variation in sensitivity of the rat diaphragm for insulin in 48 experiments. Every experiment consisted of five replicates

	Number	Effect of pure insulin upon glucose uptake (mg. glucose/100 mg. wet tissue/90 min.) observed from: 10^{-4} U/ml.	10^{-3} U/ml.
Total number of experiments	48		
Discarded on account of insignificant effects of pure insulin	8		
Abnormal high effects of pure insulin	1	$a=0.233\pm0.065$	$b=0.411\pm0.79$
Remaining experiments: mean value of a, resp. b $\pm$ stand.-deviation	39	$a=0.076\pm0.033$	$b=0.175\pm0.052$
Mean value of sdp_a, resp. and sdp_b	39	$sdp_a=0.036$	$sdp_b=0.051$
Mean value of slope of regression line	39	1.38 ± 0.44 (n=39)	

$a\pm sdp_a$ = mean value $\pm$ standard deviation of effect of 10^{-4} U/ml. in one experiment.
$b\pm sdp_b$ = mean value $\pm$ standard deviation of effect of 10^{-3} U/ml. in one experiment.

slopes of the regression lines have been calculated also from these experiments; the mean value was 1.38 $\pm$ 0.44.

As a result of the rather large standard deviations of the effects of insulin and of serum on glucose uptake and because the relationship between the effect observed and the concentration of insulin to be determined is a logarithmical one, the reliability of the estimation of serum insulin is rather small.

Randle showed that in his experiments and using his method of calculation the limits of error (at the 5 per cent level of probability) for the calculated value of serum insulin were about one-third of and three times the value found. This means that for a calculated serum insulin concentration of 3 mU/ml. the limits of error are 1 and 9 mU/ml. In our experiments the limits of error have not been calculated but are very probably of the same order.

INSULIN ACTIVITY OF SERUM IN HEALTH AND DISEASE

In our previous papers only a few figures for the insulin activity of human serum from healthy persons and patients were given. In the last three years we have tested some fifty sera with the technic described above. Calculations were made as described and the insulin activity expressed as milli-units of insulin per ml. of serum. The results are collected in figure 2.

Normal human serum. Fourteen samples of serum have been tested. Twelve of them were obtained from patients who did not suffer from any disease interfering with carbohydrate metabolism. Their blood was taken one or two days before they left the hospital after recovery. One sample was obtained from one of the investigators and one from a healthy child of three years old. The blood was taken fasting and in the

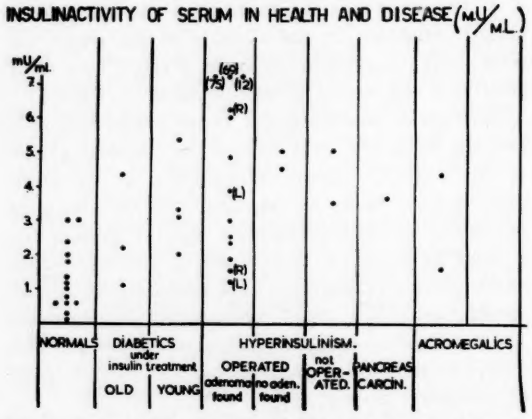

FIG. 2. Serum insulin activity in health and disease, expressed as milliunits (=10^{-3} U) of insulin per ml. of serum determined by the rat diaphragm method.

resting state. After clotting in the icebox the blood was centrifuged rapidly and the serum kept at -4° C. till the assay. The values found for these normal samples (figure 2, column 1) range from 0.1 to 3.0 milli-units of insulin per ml. of serum. The range of normal figures is therefore higher than recorded previously by us. These normal values are also considerably higher than those given by Vallance-Owen et al., who found always less than 0.1 milli-units of insulin per ml. of plasma in the fasting state. Randle on the other hand reported values ranging from 10-20 mU per ml. in the plasma of healthy individuals taken two and a half hours after they had received 50 gm. of glucose by mouth under normal working conditions.

It is not clear how these great discrepancies in normal values must be explained. Randle and Vallance-Owen et al. use plasma for the determination while we use serum. This however does not seem of great im-

portance in this connection, for it was found by Randle[11] as well as by ourselves[12] that serum and plasma, taken at the same time from the same patient, showed no significant difference in insulin activity. A factor of perhaps more importance may be the effect of the glucose given by Randle two and a half hours before blood was drawn. Vallance-Owen reported an almost tenfold increase in plasma insulin one hour after 50 gm. of glucose orally. We are at present investigating this possibility, which might be of some importance, but it does not seem probable that it gives the explanation of the above mentioned discrepancies. The possibility remains that the differences are due to small differences in technic between the laboratories. To test this a sample of lyophylized normal human plasma prepared by Randle was assayed for insulin activity by Randle in Cambridge and by us in Amsterdam. Randle found 3.2 mU and we 2.6 mU/ml. of original plasma, figures that agree very well. In a lyophylized sample of plasma taken from an acromegalic patient, however, we found only 4.4 mU/ml. whereas Randle found 121 mU/ml.

It can be said, therefore, that the reason why the insulin values found in human plasma with the aid of the test by different authors vary so widely is still unknown.

Diabetics under insulin treatment. We examined the serum from seven patients suffering from diabetes under insulin therapy. Three of them were elderly women without ketosis who took only moderate amounts of insulin. The four others were young people who developed ketosis rapidly when insulin therapy was interrupted and who required more insulin to control the disease. The blood of all these patients was taken 12 to 18 hours after the last insulin injection. In column 2, figure 2, are given the values found in the old and in column 3 the values found in the young patients. All values were well above 1 mU/ml., ranging from 1.1 to 5.2 mU/ml. of serum.

From these figures it is not possible to conclude that there is a significant difference between the serum insulin content of these two groups of diabetics, at least when they are both receiving insulin.

However Bornstein and Lawrence,[13] using hypophysectomized-alloxan diabetic-adrenalectomized rats as test animals, and more recently Vallance-Owen, Hurlock and Pease,[4] using the rat diaphragm test, reported that they have found differences in serum insulin. The latter authors observed that in their diabetics who did not require insulin (most of them older obese women who did not develop ketosis rapidly), plasma insulin activity was as high or even higher than in normal individuals. On the other hand the plasma of most, but not of all, insulin-requiring diabetics did not stimulate the glucose utilization of the rat diaphragm, especially not when the blood sugar level was well outside the physiological range. Neither was any insulin activity detectable when small amounts of pure insulin were added in vitro to the plasma of these patients. The activity of added insulin appeared to be inhibited by the plasma in these cases.

Up till now we have not been able to confirm these observations; more especially we have found, at least in the rat diaphragm test, no evidence for the presence of an insulin inhibitor in the serum of diabetic patients, even if the blood was taken during coma.

Hyperinsulinism

During the last three years we had the opportunity to examine the serum of some fifteen patients who were suspected of suffering from hyperinsulinism. All patients had hypoglycemic attacks especially when fasting. Many of them had mental disturbances during the attacks. The serum insulin determinations were carried out on blood taken during hypoglycemic attacks, when possible.

Thirteen of these patients were operated. In eleven of these thirteen cases the diagnosis of islet adenoma of the pancreas was confirmed; in some instances rather large adenomas could be removed, in other cases partial or complete pancreatectomy was performed and histological examination of the resected part of the pancreas revealed adenomatous tissue. The results of the tests on insulin activity performed with the serum of these eleven patients before the operation are given in figure 2, column 4. Seven of these values are definitely above the highest one found for normal serum (3 mU/ml.). The four others overlapped with the upper normal range.

In two operated cases no adenomatous tissue was found in the part of the pancreas that had been removed, though the condition of these patients improved after the operation. The serum insulin activity in these two cases was increased, viz 5 and 4.5 mU/ml. (figure 2, column 6).

The two remaining patients were children. They have not been operated so far. The insulin activity of their sera was 3.4 and 5.0 mU/ml., respectively (see figure 2, column 6). We examined the blood serum of one patient with a carcinoma of the islets of the pancreas who also suffered from hypoglycemic attacks. His blood serum insulin activity was found to be 3.6 mU per ml. (figure 2, column 6).

These findings with the serum of patients suspected to suffer from hyperinsulinism show that the determi-

nation of serum insulin may be of value in the diagnosis of this disease. In four cases the insulin activity of the serum sample was within the upper normal range. It should be mentioned, however, that in two of these cases (column 4, L. and R.) the insulin content of two serum samples was determined. One of these showed a normal, the other a high value. It cannot be excluded that this discrepancy was due to the limited accuracy of the procedure, but it is also possible that the insulin activity of serum of patients with hyperinsulinism varies from day to day, so that it may be necessary to perform the determinations on more than one occasion.

SUMMARY

The insulin activity of blood serum in health and disease can be determined in vitro by the rat diaphragm method as described previously. The normal fasting values range from 0.1-3 milli-units per ml. of serum. In diabetics under insulin treatment the serum insulin values were found to be normal or slightly elevated. In 9 of 11 cases of hyperinsulinism significantly increased insulin activity was found.

The method, although apparently able to detect gross changes in insulin content, as occurring in pathological conditions, is still insufficiently accurate for the study of smaller fluctuations in plasma insulin activity under physiological circumstances. Most disturbing is the fact that the values, reported by different investigators for the normal serum insulin activity, vary widely. The elucidation of the cause of this variation may lead to further improvements of the method.

SUMMARIO IN INTERLINGUA

Determination del Nivello Seral de Insulina per Medio del Methodo de Diaphragma de Rattos

Le activitate insulinic de sero sanguinee in sanitate e morbo pote esser determinate in vitro per le previemente describite methodo a diaphragma de rattos. Le normal valores in stato jejun varia ab 0,1 a 3,0 milli-unitates per ml de sero. In diabeticos sub tractamento insulinic, le valores del insulina seral se monstrava normal o levemente elevate. In 9 ex 11 casos de hyperinsulinismo, significative augmentos del activitate de insulina esseva constatate.

Le methodo, ben que apparentemente capace a deteger grossier alterationes del contento de insulina occurrente in conditiones pathologic, es ancora insufficientemente accurate pro le studio de minor fluctuationes del activitate de insulina in le plasma sub conditiones physiologic. Le plus disquietante facto es que le valores reportate per varie investigatores pro le normal activitate de insulina seral exhibi grande variationes. Le clarification del causas de iste variationes va possibilemente resultar in meliorationes additional del methodo.

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Effect of Proteins on the Blood Glucose Levels

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The yield of glucose obtained in protein metabolism is approximately 50 per cent of the weight of ingested protein (Reilly, Nolan and Lusk 1898,[1] Ringer and Lusk 1910,[2] Janney and Csonka 1915,[3] Janney 1916[4]). Janney (1915)[5] found that with isolated proteins the production of glucose varied from 48 per cent to 80 per cent, whereas Bancroft and Drury (1951)[6] in the phlorizinized-depancreatized dog observed a 90 to 95 per cent conversion of protein to glucose. The liberation of glucose into the blood stream during protein metabolism is slower than the liberation of an equivalent amount of glucose derived from glucose and carbohydrate foods, shown by Conn and Newburgh (1936)[7] in experimental studies with fifteen diabetic patients. Pollack and Dolger (1938,[8] 1939[9]) suggested the diabetic patients take 50 per cent or more of the daily protein allowance at the evening meal in order to buffer the tendency toward decreasing blood sugar concentration during the night. Gubbay (1951)[10] found that in feeding diabetic patients with protein, the slow conversion of protein to glucose caused minor changes in the blood sugar of well controlled diabetic patients.

The purpose of the present study was to investigate the changes in level of blood glucose, after feeding normal and diabetic human subjects with various amounts of isolated plant proteins, gelatin and egg white. Eighty normal and eight diabetic volunteers were the subjects of the present study. A total number of 176 experiments were performed studying the effect of the whole egg white, gelatin, and proteins prepared from lentil, oat, wheat and pea bean. The details of the experiments and the results obtained are described in the present paper.

MATERIALS AND METHODS

Preparation of plant proteins. After grinding the plant food, the fat was extracted in a Soxhlet's apparatus. The residue was suspended in a 10 per cent aqueous solution of sodium chloride. The mixture was stirred for several hours and allowed to settle. The clear water solution was decanted. A fresh 10 per cent sodium chloride solution was added, the solution stirred, and again decanted. The above process was repeated until no appreciable amount of proteins could be detected in the salt solution. The saline layers were combined and filtered in order to remove impurities. Acetic acid was added to the filtrate in a final concentration of about 80 mM. The resulting mixture was heated to the boiling point. After cooling, the precipitated protein was filtered and washed with water. The protein was collected and dried in an oven at 60°C.

Digestibility of proteins. The digestibility of the obtained proteins was determined by Steudel's method (1935).[11] The materials to be tested were examined for water, ash, nitrogen and caloric content (original values). The materials digested in vitro and the undigested residue were again submitted for determination of ash, nitrogen and caloric content. The calculations were referred, in both cases, to 100 gm. of the original substance and the difference of both results yields the utilized part of the sample tested. The samples (100 gm. in 1,000 ml. of water) were digested with the different enzymes: Pepsin 0.5 gm. 8 ml. concentrated HCl, pancreatin 0.4 gm. 2 gm. sodium carbonate and diastase 0.05 gm. made slightly alkaline with sodium carbonate. For this purpose they were left in 1,000 ml. of water saturated with toluene for forty-eight hours in an incubator at 37° C. with frequent stirring. The remaining residue after centrifuging comprises the undigested part of the material.

The changes in the glucose content of the subject's blood after feeding the individual protein was investigated as follows: After fasting twelve hours the subjects were fed a known amount of the individual protein. The glucose content of the subject's blood was determined beforehand using the Hagedorn-Jensen method (1923).[12] Duplicate determinations were made at intervals of three and a half and five hours after feeding the proteins. The subjects remained in a reclining position after the intake of the proteins without additional nutriment. Goth, Bencze and Lengyel (1952)[13] used the same method in

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studying the dietary effect of egg whites on the blood glucose levels of humans with an adrenal cortex insufficiency.

Any change of less than 10 mg. per cent in the glucose of the blood was considered negligible.

EXPERIMENTAL RESULTS

The subjects of the experiments were volunteers of the Evangelismos Hospital of Athens, Greece. The average age was 35 (20 to 50). The diet served by the hospital was generally the same for all the subjects. The test started in the morning about 8:30 a.m. and ended five hours later. The subjects who were tested with the individual plant protein were tested again the next morning under the same conditions, with 20 gm. of egg white dried at 60° C. This was used as a standard control for all the experiments. Eight volunteer diabetic patients were tested under experimental conditions just described. For a week previous to the experiment they were not treated with insulin or other drugs. A glucose tolerance test was performed on each of these patients to confirm the diagnosis of diabetes. Control experiments were performed with 20 gm. dried egg white.

The analytical data of the obtained results for the tested proteins, for both normal and diabetic subjects, are described as follows:

Egg white. Feeding 14 gm. of egg white there was no increase in blood glucose. Upon increasing the amount of egg white from 17 gm. to 23 gm., an increase in glucose of 10 to 30 mg. per 100 ml. of blood was observed after three and a half and five hours; in some individual cases the glucose remained unchanged. The amount of 20 gm. of egg white was selected as a standard control for comparing the obtained results after feeding the subjects with plant proteins. In a total number of sixty-three tests with normal subjects feeding 20 gm. of egg white, (tables 1-4), the average increase of the glucose was 14.6 mg. per 100 ml. of blood, with individual increases of 10 to 40 mg. per cent. A similar result was obtained feeding eight diabetic subjects with 20 gm. of egg white. The average increase after five hours was 12.3 mg. per cent (table 4).

Oat protein. Normal subjects were fed 15 to 25 gm. oat protein, and a decrease or unchanged blood glucose was observed after three and a half and five hours. After feeding 30 to 36 gm. there was an increase of 10 to 40 mg. in glucose per 100 ml. of blood. The average increase after feeding five subjects with 36 gm. oat protein was 14.4 mg. per cent. In three cases the glucose remained unchanged (table 1). Oat protein was tested in three diabetic subjects by feeding 13 gm. and 20 gm. oat protein. In all cases there was a decrease in blood glucose (table 4).

Wheat flour protein (gluten). The protein fed to thirteen normal subjects was the gluten of the wheat. The subjects were fed 15 to 30 gm. gluten and no increase of the blood glucose was observed. After feeding 32 to 40 gm. of gluten, an increase in glucose of 10 to 40 mg. per 100 ml. of blood was obtained. The average increase by feeding four subjects with 40 gm. was 21.9 mg. (table 1). Four diabetic subjects were fed 20 to 35 gm. of protein. An increase of blood glucose was observed three and a half hours after feeding 35 gm. of gluten (table 4).

Lentil protein. The subjects fed 20 to 55 gm. of lentil protein showed no increase in blood glucose. Feeding 64 gm. to 70 gm. an increase of glucose was observed in the subject's blood; in four cases there was no change in glucose. Four subjects fed 70 gm. lentil protein showed an average increase of 16.5 mg. per 100 ml. of blood (table 2). Diabetics were not tested with lentil protein.

Pea bean protein. Nineteen subjects were fed with pea bean protein. It was necessary to feed about four times as much pea bean protein as egg white so that an increase in blood glucose could be obtained. The average increase, feeding three subjects with 78 gm. pea bean protein, was 18.6 mg. per 100 ml. of blood (table 3). In one case, feeding the diabetic subject with 25 gm. of pea bean, there was no change in glucose levels.

Gelatin. Gelatin fed in seven normal subjects from 15 to 30 gm. showed no increase in blood glucose.

The results suggest, as is shown in tables 1 to 4, that the amount of protein required to produce an increase in level of blood glucose in normal subjects, varies with the protein employed. Seventeen grams to 23 gm. egg white seems to be enough to produce an increase, whereas for a similar result 30 to 36 gm. of oat protein are necessary, 32 to 40 gm. of wheat (gluten) protein, 64 to 70 gm. for the lentil protein, and 72 to 78 gm. for the pea bean protein. The gelatin tested in the amount of 30 gm. showed no increase in blood glucose.

The digestibility of the tested proteins, determined with Steudel's (1935)[11] method, was found as follows: Egg white, 100; Oat protein, 90; Wheat flour (gluten), 91; Lentil protein, 86; Pea bean protein, 80.

DISCUSSION

Determination of the glucose in the blood of normal and diabetic human subjects, three and a half and five hours following the ingestion of different proteins, suggests that egg albumin has the highest rate of conversion to glucose followed by oat protein, wheat protein (gluten), lentil protein, and pea bean protein. This may

TABLE 1

Effect of oat and wheat flour protein on the blood glucose

Dose gm.	Test substance: Oat protein mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose	Egg white control (20 gm.) mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose
15	86	101	86		90	90	100	
"	79	69	79	1.2	76	98	106	
23	82	82	82		78	118	108	
"	100	90	90		97	97	112	
"	67	77	77	0.0	78	103	98	
30	78	105	78		86	86	86	
"	116	116	116		98	118	108	
"	79	89	79	6.2	83	110	110	
36	86	113	124		79	94	94	
"	96	96	86		106	106	106	
"	78	95	95		69	94	89	
"	78	100	88		78	105	105	
"	97	124	97	14.4	86	76	76	16.3
	Test substance: Wheat flour protein							
15	98	98	88		87	77	97	
"	75	75	75		79	109	94	
"	87	97	72	−2.5	76	86	96	
25	106	116	106		97	124	97	
"	115	115	105	0.0	86	101	101	
32	93	93	103		100	110	100	
"	80	70	70		87	87	97	
"	78	78	78		76	106	103	
"	83	98	83	0.6	98	98	98	
40	92	116	114		79	119	114	
"	87	87	77		83	83	83	
"	85	117	117		96	111	111	
"	78	118	93	21.9	85	107	117	14.2

TABLE 2

Effect of lentil protein on the blood glucose

Dose gm.	Test substance: Lentil protein mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose	Egg white control (20 gm.) mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose
20	97	97	82		83	113	108	
"	106	116	106	−1.2	97	97	107	
35	89	79	79		76	76	96	
"	83	93	83	−2.5	87	87	77	
45	78	88	78		78	110	105	
"	94	104	79		86	126	116	
"	116	106	116	−0.8	93	83	103	
55	86	91	76		76	136	116	
"	95	95	95	1.2	89	104	104	
64	76	91	86		85	70	90	
"	96	106	96		106	106	106	
"	78	78	78		76	106	96	
"	89	89	89		83	110	115	
"	82	102	92	3.8	96	106	96	
70	86	126	118		87	92	92	
"	100	100	115		107	107	107	
"	76	94	103		79	106	106	
"	78	78	78	16.5	89	99	89	14.6

TABLE 3

Effect of pea bean protein on the blood glucose

Dose gm.	Test substance: Pea bean protein mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose	Egg white control (20 gm.) mg. glucose in 100 ml. blood 0 hr.	3½ hr.	5 hr.	Mean change per dose
20	86	76	86		75	90	90	
"	82	72	72	−7.5	86	96	86	
30	93	83	103		95	95	105	
"	78	78	78		69	101	96	
"	72	82	72	2.5	78	93	105	
50	103	93	93		95	95	80	
"	97	107	97	−2.5	88	78	88	
60	80	107	80		75	105	105	
"	93	93	83		82	109	97	
"	100	100	100	2.8	92	82	107	
65	85	85	85		79	94	94	
"	86	86	76		80	107	107	
"	75	75	75	1.6	72	104	99	
72	106	106	116		98	108	88	
"	79	79	79		87	72	87	
"	95	95	115	8.3	82	122	114	
78	86	86	106		75	107	107	
"	78	78	88		83	98	93	
"	76	76	91	18.6	78	105	93	14.8

TABLE 4

Effect of various plant proteins on the blood glucose level of diabetics

Protein	Dose gm.	Test substance: Plant protein mg. glucose in 100 ml. blood 0 hrs.	3½ hrs.	5 hrs.	Egg white control (20 gm.) mg. glucose in 100 ml. blood 0 hrs.	3½ hrs.	5 hrs.	Mean change per dose
Oat	13	216	186	176	198	198	198	
"	20	245	235	205	230	230	206	
"	20	182	152	152	167	182	182	
Wheat	20	162	138	132	185	185	185	
"	25	206	191	168	178	183	178	
"	30	166	151	166	160	175	175	
"	35	145	167	155	132	192	164	
Pea bean	25	182	182	182	165	192	192	12.3

be due to the different rate of time required for each protein to liberate glucose into the blood stream and to the fact that the yield of glucose per unit weight of protein varies from protein to protein. There was no significant effect on the blood sugar levels of the tested diabetics, although greater doses of plant proteins are necessary in order to obtain more conclusive results.

Proteins ingested in an impure state with cellulose and other impurities are less digestible than in a pure, very finely divided form (Janney).[5] The amount of water ingested with the protein meal also has an effect on the rate of digestion. However, the conditions of preparation of the tested proteins, and those of the experiments, eliminate the effect of these factors. The test for the blood glucose in periods of three and a half and five hours after ingestion of the proteins also eliminates the possibilities of error from nonspecific factors. Janney (1915)[5] noticed that the glucose excretion reaches its maximum at the second to the third hour after intake of the protein; complete elimination of the glucose occurs by the ninth hour. However, it is true that the proteins used for these experiments are denatured and although they are digestible, their reactions might be different from the equivalent undenatured products. Changes in level of blood glucose were sometimes as great as 40 to 60 mg. per 100 ml. of blood. This is considerably greater

than could be explained by experimental error (±10 per cent).

SUMMARY

An increase of glucose in the blood of normal and diabetic human subjects was determined at three and a half and five hours following the ingestion of different proteins. The data suggest that egg albumin has the highest rate of conversion to glucose, followed by oat, wheat flour (gluten), lentil, and pea bean proteins. There was no significant effect on the blood glucose levels of the tested diabetics.

SUMMARIO IN INTERLINGUA

Nivellos de Glucosa del Sanguine in Humanos Normal e Diabetic Post Ingestion de Proteinas Animal e Vegetal

Un augmento del glucosa del sanguine in humanos normal e diabetic esseva determinate 3½ e 5 horas post le ingestion de varie proteinas. Le datos suggere que albumina ab ovos ha le plus alte proratas de conversion in glucosa. Illo es sequite per proteinas ab avena, farina de tritico (glutine), lenticula, e faba sic. Esseva notate nulle significative effecto super le nivellos de glucosa sanguinee in le diabeticos testate in iste studio.

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Somatotypes

Elsewhere we have discussed the question of classification of the body according to "somatotype" and the application of this to nutritional problems.[1, 2] Though it is admitted that there are, in fact, body types independent of body weight and fatness and that this fact ought to be brought into the analysis somewhere, the fact is that no acceptable scheme is yet at hand. Sheldon's[3] "endomorphy" and "ectomorphy" appear to be primarily impure expressions of the obesity-emaciation continuum,[4, 5, 6] while the meaning of "mesomorphy" is uncertain. The fact that Sheldon's somatotypes are related to body fatness and to total body water[7, 8] does not confer any special value to somatotyping; better estimates of these items are available by other means.

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Effect of Insulin on Glycosuria, Polyuria and Food Intake in Alloxanized Rats

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INTRODUCTION

In recent studies of the quantitative relationships among glycosuria, food intake and body weight in alloxan-diabetic rats, we utilized an index of disturbance in glucose metabolism that was independent of variations in food intake and body weight.[1] This index was expressed as the ratio of glycosuria to food intake, which is readily converted to the percentage dietary carbohydrate that is utilized. Utilization thus calculated was found to be significantly increased by adrenalectomy and reduced by lethal doses of cortisone or thyroxin.[2] Sublethal doses of cortisone or thyroxin, adrenocorticotrophic hormone, diethylstilbestrol, cobaltous chloride, and partial thyro-parathyroidectomy-thiouracil treatment had no significant effect.[2] Starvation[1] and treatment with an anorexigenic drug[3] (nitrogen mustard) were also ineffective. The change in carbohydrate utilization, averaged over five days of treatment with insulin, was linearly related to the log dose of insulin.[3] The present report details the temporal progression of glycosuria, polyuria, food intake, body weight, and the calculated carbohydrate utilization before and during the time of insulin administration.

MATERIALS AND METHODS

Routine Alloxanization Procedure. Male Sprague-Dawley rats, 120 to 160 gm. body weight and fed granulated Rockland Rat diet and tap water ad libitum, are injected intraperitoneally with 160 mg./kg. body weight of a freshly prepared, 1 per cent aqueous solution of alloxan monohydrate (Eastman) on Monday and again on Wednesday. On Friday, urine is collected for twenty-four hours. Those rats with a urine volume less than 30 ml. receive a third injection of alloxan the following Monday; those failing to respond with polyuria to this injection are discarded. All of the remaining alloxanized, supposedly-diabetic rats are then kept for three weeks before collecting another twenty-four-hour urine sample for glucose analysis and confirmation of diabetes. During this three-week interval, some rats show remissions of glycosuria, while the remainder develop a fairly stable diabetic state as indicated by a plateau in glucose excretion.[4] At this time, variations in food intake and body weight account for nearly 88 per cent of the variability in glycosuria.[1] The rats are never starved before alloxan injection[5] because we have found this procedure to increase mortality disproportionately to the increase in the number of diabetics produced. Substitution of 1 per cent glucose solution for tap water, or glucose injection,[6] in order to prevent fatal post-alloxan hypoglycemia,[7] has been of such slight benefit to us that it is not believed to be worth while.

A summary of the results of alloxanization of twenty representative series of approximately fifty rats each follows: 1,024 rats received the first and second injections of alloxan, after which 61 (6.0 per cent) died. Of the survivors, 484 (47.3 per cent) developed a permanent diabetes and the 479 (46.8 per cent) alloxan-resistant rats received the third injection. Of these 479, 160 became permanently diabetic. Therefore, from 1,024 rats, a total of 644 (62.9 per cent) diabetics was obtained. These data do not support previous observations that the ED_{50}[8] and the LD_{50}[9] for alloxan are essentially the same.[10]

Experimental. Thirty-five diabetic rats, prepared as above, were placed in individual, paraffin-coated, metabolism cages and offered tap water and a medium carbohydrate diet[1] ad libitum. Spilled drinking water was trapped to prevent dilution of the urine; the diet was given in the form of a thick paste to minimize spillage. The maximal available glucose and energy contents per gram of dry diet were calculated from all nutrients as 0.64 gm. and 4.8 kcal. respectively. Urine was collected daily under toluene and analyzed for glucose by a modification of the Hanes-Hagedorn-Jensen method. Glycosuria (G) was recorded daily for each rat in grams glucose, urinary glucose concentration in gm./L., urine volume in ml., food intake (I) in grams dry food, and body weight in grams.

After ten days of control observations, each rat re-

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ceived seven daily subcutaneous injections of protamine zinc insulin (Lilly), 10 U/kg. body weight. For purposes of calculation, the data obtained the first three control days were omitted in order to delete any variations attributable to adaptation of the rats to the experimental conditions.

On each day of observation, the glucose excretion of each rat was divided by the intake of available glucose (0.64I) to obtain the percentage excreted (100G/0.64I); subtraction from 100 yielded percentage utilization. These percentages, as well as the glycosuria, urinary glucose concentration, urine volume, food intake, and body weight, were then averaged for all of the rats on each day.

RESULTS AND DISCUSSION

During the pretreatment week, glycosuria (G) was significantly related to food intake (I) and body weight (W). The respective regression equations, calculated from the thirty-five means of the last five pretreatment days, were as follows: $G = -0.73 + 0.359\ I$ and $G = 4.79 + 0.016\ W$. These relationships compared favorably to those obtained in previous experiments.[1, 2] Also during this week, the daily mean urine volumes and urinary glucose concentrations remained fairly constant, averaging approximately 115 ml./day and 75 gm./L., respectively (figure 1); however, during the week of insulin administration, these values progressively decreased to approximately 20 ml. and 20 gm./L. on the seventh day. Cohen[11] has shown that the urinary glucose concentration of alloxan-diabetic rats increases progressively with urine volume until a limiting value of 60-80 gm./L. is attained, whereafter the concentration plateaus. This ceiling of renal concentrating ability is reached at a blood sugar level of approximately 300 mg./100 ml. Our data confirm Cohen's observations.

As a result of the decrease in glucose concentration and urine volume (figure 1), glycosuria fell from a pretreatment average of 8.4 gm./day to 0.4 gm. on the final day (figure 2). The regression of glycosuria on urine volume was linear and without a plateau, again confirming Cohen's results. The percentage excretion of available dietary glucose tended to parallel glycosuria because of the relative constancy of food intake: while the percentage excretion dropped from a pretreatment average of 50.9 per cent to a final value of 2.8 per cent (table 1), the food intake ranged between 24 and 30 gm./day both before and during insulin therapy (means: 27.1 and 26.8 gm./day, respectively). In other words, the untreated diabetic rats utilized almost 50 per cent of their consumption of 68 gm. available glucose/

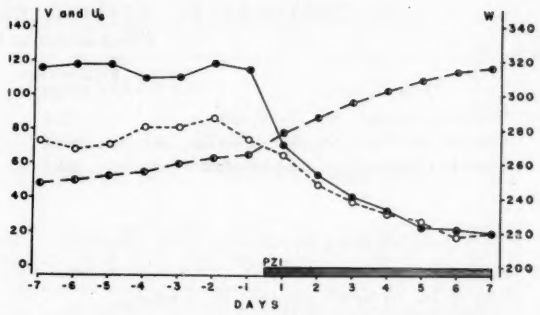

FIG. 1. Temporal responses to 10 U/kg./day of protamine zinc insulin (PZI) of alloxan-diabetic rats. Urine volume in ml. (V: solid circles), urinary glucose concentration in gm./L. (UG: open circles), and body weight in gm. (W: halved circles).

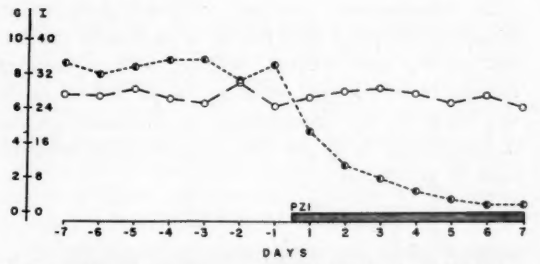

FIG. 2. Temporal responses to 10 U/kg./day of protamine zinc insulin (PZI) of alloxan-diabetic rats. Glycosuria in gm. (G: halved circles) and dry food intake in gm. (I: open circles).

kg. body weight/day, while seven days of insulin-treatment increased utilization to 97 per cent of the intake of 49 gm. glucose/kg./day. Notwithstanding the constant food intake, gain in body weight rose from a pretreatment average of 2.4 gm./day to a treatment average of 5.6 gm./day (table 1); the nature of this acceleration was not determined.

It is of interest to compare our results to those obtained by Dohan, Fish, and Lukens[12] on anterior pituitary-diabetic dogs fed raw beef heart ad libitum. Insulin treatment reduced to practically nil the urinary excretion of 80 to 90 per cent of the available glucose consumed without markedly altering the food intake. It is also desirable to compare our figures to those derived by Stetten, Welt, Ingle, and Morley[13] from experiments on several fasted, anesthetized, alloxan-diabetic and normal rats, previously force-fed. Under intravenous glucose infusions, their diabetic rats utilized 39 per cent as much glucose as the normals. This figure seems in fair agreement with ours of 50 per cent considering the differences in experimental approach.[14] Comparable

TABLE 1
Effect of insulin in alloxan-diabetic rats

Daily Values	Pretreatment Mean	Days of Insulin Therapy						
		1	2	3	4	5	6	7
Weight gain, gm./day	2.4	12.8	9.4	9.0	7.0	5.4	5.6	2.6
Glucose excretion, per cent of intake	50.9	27.0	14.7	11.4	6.7	5.0	2.9	2.8
Glucose retention, per cent of intake	49.1	73.0	85.3	88.6	93.3	95.0	97.1	97.2

results were obtained by Chernick and Chaikoff,[15] who found the oxidation of added glucose by diabetic liver slices to be 10 to 60 per cent of normal.

SUMMARY

A detailed description is given of the procedure used to induce alloxan diabetes in 1,024 rats with a 63 per cent success.

In alloxan-diabetic rats fed ad libitum, daily insulin therapy caused progressive falls in urine volume, glucose, and glucose concentration, together with a transient increase in weight-gain. Since no change in food intake was observed, the improvement in calculated glucose utilization (49 to 97 per cent) paralleled the improvement in glycosuria.

SUMMARIO IN INTERLINGUA

Effectos de Insulina Super Glycosuria, Polyuria, e Ingestion de Alimentos in Rattos Alloxanisate

Es presentate un description detaliate del technica usate pro inducer diabete a alloxano in 1.024 rattos. Le methodo succedeva in 63 pro cento del animales.

In rattos con diabete alloxanic, mantenite sin restriction de dieta, un diurne therapia a insulina causava progressive reductiones del volumine de urina, del glucosa, e del concentration de glucosa, insimul con un transiente acceleration del augmento de peso. Nulle alteration del ingestion de alimentos esseva observate, e le melioration del calculate utilisation de glucosa (ab 49 usque a 97 pro cento) esseva parallel al melioration del glycosuria.

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Studies on Humoral Insulin Antagonists in Diabetic Acidosis

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with the technical assistance of Minnie L. Woodson, B.S., Bethesda, Maryland

In a previous paper an antagonist to insulin was described in the sera of patients in diabetic acidosis.[1] This factor was thought to be independent of the adrenal cortical hyperactivity and the lowered serum *p*H usually accompanying diabetic coma. Groen et al.[2] had reported previously that sera obtained from patients in diabetic acidosis were devoid of any insulin activity, but insulin added to such sera exerted its anticipated effect on the glucose utilization by the rat diaphragm. Consequently, these investigators concluded that the absence of an insulin effect in serum during diabetic acidosis was not attributable to an insulin antagonist. More recently Vallance-Owen et al.[3] have found that insulin added to plasma from diabetic patients requiring insulin and having a high blood sugar, but not in ketosis, did not increase the glucose utilization of the rat diaphragm. However, in these same patients when the blood sugar was normal, insulin added to the plasma exerted its usual effect. These authors suggest that many diabetics require insulin to overcome an insulin inhibitor in their plasma.

The present report concerns further studies which have been done to characterize the insulin antagonist found during diabetic acidosis.

METHODS

The method for determining the insulin effect was the same as was used previously[1] and is based on the ability of insulin to augment the glycogen deposition by the rat hemidiaphragm. Briefly, one hemidiaphragm was exposed to 1 ml. of serum and 1 ml. of 0.04 M phosphate-saline buffer (*p*H 6.8) containing 0.2 unit insulin for one minute while the control hemidiaphragm was exposed to only serum and buffer. Each hemidiaphragm was then washed twice in buffer solution and incubated for ninety minutes in a solution containing 0.4 per cent glucose in the same buffer. At the end of the incubation the glycogen content of each hemidiaphragm was determined. The increase in glycogen content in the rat hemidiaphragm exposed to insulin, expressed as μmole of glucose per gm. of diaphragm, is referred to as the insulin effect.

Sera used in the experiments were obtained from patients in diabetic acidosis at the time of their admission to the hospital before they had received any insulin therapy. In some cases a later specimen was obtained several hours after treatment for acidosis had been instituted. Serum was kept frozen at —4°C for many months without any loss of its ability to antagonize insulin.

Electrophoretic separation of the serum into its various protein components was done by continuous paper electrophoresis in a temperature-control apparatus at 8° C for thirty-six hours according to the method of Saroff.[4] The buffer system was sodium barbiturate of ionic strength 0.08 and *p*H 8.6. The current was 46 milliamperes and a double thickness of 12-inch sheet of Whatman #3 paper was used. The identity of the protein component in each fraction collected was determined by independent paper strip electrophoresis in the barbiturate buffer at room temperature for twenty-two hours using a current of 10 milliamperes and Whatman #1 paper. After the electrophoresis the strips were dried at room temperature and stained with bromphenol blue.

Lipoproteins were obtained by centrifugation of serum in the preparative ultracentrifuge at 15° C and 114,400 x *g* for eighteen hours. Prior to centrifugation, the density of the serum was adjusted to 1.21 by the addition of concentrated sodium chloride. Both the separated lipoproteins and the remainder of the serum were dialyzed for four hours against 0.04 M phosphate-saline buffer to reduce the salt concentration before they were each assayed in the rat hemidiaphragm system.

I^{131} labeled insulin was obtained from Abbott Laboratories and was dialyzed overnight against 0.04 M phos-

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phate-saline buffer at 14° C. At the end of dialysis 99 per cent of the radioactivity was trichloroacetic acid precipitable. The binding of insulin to the rat hemidiaphragm was measured as follows: After being weighed, one hemidiaphragm was exposed to 0.2 ml. of normal serum and 2 ml. of 0.04 M phosphate-saline buffer containing 0.2 units of nonlabeled insulin and 0.01 units of insulin-I^{131} with a total of 100,000 counts per minute. The other hemidiaphragm was exposed to a similar mixture except that 0.2 ml. of insulin antagonist serum was substituted for the normal serum. This amount of serum was capable of antagonizing the effect of 0.2 unit of insulin.[1] After one minute exposure each hemidiaphragm was washed twice in 30 ml. of phosphate-saline buffer for thirty minutes and then counted in a scintillation counter. The amount of insulin bound is expressed as counts per gram of tissue. Using this procedure, Stadie et al. have shown that insulin is rapidly and firmly bound to the hemidiaphragm and cannot be washed out.[5]

The presence of insulinase activity in the insulin antagonist serum was tested for by the procedure of Vaughan:[6] 0.2 ml. of normal serum and 0.2 ml. of antagonist serum were each incubated for sixty minutes at 37° C in 2 ml. of 0.1 M phosphate buffer (*p*H 7.4) containing 10 units of nonlabeled insulin and 0.001 units of insulin-I^{131}. At the end of the incubation the proteins were precipitated with an equal volume of 20 per cent trichloroacetic acid and the radioactivity in the supernatant solution counted in a scintillation counter. The total amount of radioactivity present at the beginning of the incubation was also ascertained. The insulinase activity is reported as the per cent of I^{131} initially present which became soluble in trichloroacetic acid. Five tenths ml. of rat liver homogenate in distilled water was used as a control since it is known to be a good source of insulinase.[6]

RESULTS AND DISCUSSION

Chemical Nature of the Inhibitor. Insulin antagonist activity was not lost as a result of overnight dialysis against sodium barbiturate buffer (*p*H 8.6) of ionic strength 0.1 at 18° C. The dialyzed serum was then separated into its protein components by paper electrophoresis. Serum obtained from Case VII was used for this study. It had previously been shown that 0.05 ml. of this serum inhibited the effect of 0.2 units of insulin and as little as 0.01 ml. had some activity.[1] An amount of albumin equivalent to 0.1 ml. of serum did not significantly lower the insulin effect (table 1). However, when alpha-globulins were tested the insulin effect was abolished by the equivalent of 0.02 ml. of serum. There was even some suggestive effect when one-tenth of this amount was used. Beta-globulins equal to 0.1 ml. of serum were devoid of demonstrable insulin antagonist activity. Only when twice this amount was used was there evidence of insulin antagonism. The small amount of activity present in this fraction can probably be explained by the incomplete electrophoretic separation of the protein fractions. The gamma-globulin fraction was also devoid of insulin antagonist activity. This insulin antagonist is either a protein or a smaller molecule somehow bound to a protein with an electrophoretic mobility similar to the alpha-globulins. Since the activity was in the alpha-globulins rather than the gamma-globulin fraction, it is apparent that it is a different material from the antibody which has been previously reported in the sera of some patients whose insulin resistance was not associated with acidosis or infection.[7, 8, 9, 10]

TABLE 1

Activity of various protein fractions of insulin antagonist serum

Fraction	Equivalent amount of whole serum ml.	Insulin effect micromoles (glucose equiv.) per gm. of tissue Mean±S.E.M.
Albumin	0.1	5.15±0.94 (6)*
alpha-Globulins	0.02	1.12±0.94 (9)
alpha-Globulins	0.002	3.70±1.49 (6)
beta-Globulins	0.2	2.52±0.97 (3)
beta-Globulins	0.1	4.13±2.68 (3)
gamma-Globulins	0.1	6.70±1.26 (8)
Normal Serum+	1	5.35±0.48 (23)

( )* Number of determinations
+ See bibliography reference 1.

Although the alpha-globulins are known to be rich in lipoproteins, the insulin antagonist is not a lipoprotein. In the presence of this fraction obtained from insulin resistant serum, the insulin effect was 4.66 micromoles/gm. of tissue as compared to —1.25 micromoles/gm. of tissue when the remainder of the serum was used (table 2). Repeated freezing and thawing did not decrease the activity of this insulin antagonist. Table 3 indicates that the antagonist was inactivated by heating at 100° C for four minutes, but not at 60° C for fifteen minutes.

Endocrine Relationships. Since insulin refractory diabetes has been produced by the administration of growth hormone to dogs,[11] and the diabetes which occurs in association with acromegaly in humans is often insulin resistant,[12] it was thought pertinent to test sera obtained from acromegalic diabetics for insulin antagonist activity. Although these two patients showed no fall in their blood sugar levels following an intravenous injection of

TABLE 2

Absence of insulin antagonist activity in lipoprotein fraction of serum from Case VII

Fraction	Equivalent amount of serum	Insulin effect micromoles glucose equiv./gm. of tissue Mean±S.E.M.
Lipoprotein	0.2 ml.	4.66±2.60 (3)*
Remaining proteins	0.2 ml.	−1.25±1.47 (6)

( )* Number of determinations

TABLE 3

Effect of heating on the activity of insulin antagonist serum

Treatment of serum	Equivalent amount of whole serum ml.	Insulin effect micromoles (glucose equiv.) per gm. of tissue Mean±S.E.M.
Untreated	0.1	−1.03±1.17 (6)*
Heated 15 min. at 60° C	0.5	0.65±0.14 (3)
Heated 4 min. at 100° C	0.1	4.53±0.95 (3)

( )* Number of determinations

0.1 unit of regular insulin/kg. of body weight, their sera did not contain any demonstrable insulin antagonist (table 4). Since it has been reported that adrenocorticotropin (ACTH) exerts a synergistic effect on the action of growth hormone,[13] one of the acromegalic patients (A.L.) was given a forty-eight-hour intravenous infusion of 200 units of ACTH. At the end of this infusion the serum still did not exhibit any insulin antagonist activity. It thus seems unlikely that the antagonist is related to growth hormone. However, until growth hormone in serum can be assayed directly, it is not possible completely to exclude it as the cause of the increased tolerance to insulin in diabetic acidosis. Previously, we have shown that this insulin antagonist is also independent of adrenal cortical hyperactivity.[1]

Other Relationships. In two cases of diabetic acidosis it was possible to obtain serum six and nine hours, respectively, after the institution of insulin therapy. Table 5 indicates that by this time it was no longer possible to detect any insulin antagonist. Either the antagonist had disappeared from the serum at these times or it had been effectively neutralized by the insulin which had been administered as therapy for the acidosis. On the basis of information available, we are unable to decide between these two hypotheses.

Marsh and Haugaard have previously reported an insulin antagonist in the sera of diabetic patients whose insulin resistance was not associated with either acidosis

TABLE 4

Inability of serum from diabetic acromegalics to inhibit insulin effect

Source of serum	Amount of serum ml.	Insulin effect micromoles (glucose equiv.) per gm. of tissue Mean±S.E.M.
H.R. 52 yr. female	1	5.93±0.95 (6)*
A.L. 55 yr. female	1	5.24±0.64 (6)
A.L.—at end of 48 hr. infusion of 200 units ACTH	1	5.41±1.27 (6)

( )* Number of determinations

TABLE 5

Time relationship between disappearance of insulin antagonism and onset of therapy for diabetic acidosis

Source of serum	Amount of serum ml.	Insulin effect micromoles (glucose equiv.) per gm. of tissue Mean±S.E.M.
Case VIII		
9-13-55 10:00 a.m.	1	1.74±1.82 (3)*
9-13-55 7:00 p.m.	1	5.69±0.13 (3)
Case IX		
2-21-56 4:00 p.m.	1	1.40±0.43 (8)
2-21-56 10:00 p.m.	1	4.40±2.56 (3)
Normal serum	1	5.35±0.48 (23)

( )* Number of determinations

or infection.[14] They found that if the hemidiaphragm was exposed to insulin resistant serum and then was subsequently immersed in an insulin solution, there was no inhibition of the insulin effect. This indicated that the factor which they were studying in serum had to be present at the same time the diaphragm was exposed to insulin in order to exert its antagonism. In contrast to their observation, table 6 shows that the humoral factor present during diabetic acidosis was capable of inhibiting the effect of insulin whether diaphragm was exposed first to either insulin or serum. These findings indicate that the insulin antagonist in the serum during diabetic acidosis was bound rapidly and firmly by the diaphragm and then exerted its anti-insulin effect. Even if the insulin was bound to the diaphragm first, the antagonist was still capable of inhibiting its action. These experiments also show that the antagonist did not compete with insulin for binding sites on the diaphragm, nor did it exert its effect by preventing the diaphragm from binding insulin. Further support for this latter conclusion was obtained by measuring the amount of insulin-I^{131} bound to the rat diaphragm in the presence of normal and antagonist serum. Table 7 demonstrates that the same amount of insulin was bound by the diaphragm whether insulin

TABLE 6

Ability of insulin antagonist serum to abolish insulin effect when diaphragm is exposed to it and insulin separately

Procedure	Amount of serum ml.	Insulin effect micromoles (glucose equiv.) per gm. of tissue Mean±S.E.M.
Pre-exposure of diaphragm to serum	0.2	0.71±2.04 (3)*
Pre-exposure of diaphragm to insulin	0.2	1.15±0.46 (3)

( )* Number of determinations

TABLE 7

Failure of serum from insulin resistant diabetic acidosis patient to inhibit binding of I^{131}-insulin to rat diaphragm

Source of serum	Number of experiments	Counts/min. of I^{131} bound/gm. of diaphragm using I^{131}-insulin±S.E.M.
Normal	6	2,683±204
Case VII	6	2,758±144

TABLE 8

Absence of insulinase activity in insulin antagonist serum

Material	Amount ml.	% I^{131} from insulin-I^{131} in trichloroacetic acid supernatant after 60 min. incubation
Liver homogenate	0.5	57
Insulin antagonist serum	0.2	0
Normal serum	0.2	0

antagonist serum or normal serum was used.

The mechanism of action of the insulin antagonist found during diabetic acidosis cannot be attributed to any insulinase activity (table 8). Furthermore, insulinase has never been reported in the serum.[15] Since insulinase has been found in muscle,[15] it is conceivable, but unlikely, that the antagonist somehow augments or accelerates the degradation of insulin by this enzyme.

SUMMARY

The serum insulin antagonist which occurs during diabetic acidosis has been further characterized. It does not seem to be related to growth hormone secretion. In two cases studied, the antagonist was no longer demonstrable in the serum six to nine hours after the onset of insulin therapy. The activity was nondialyzable and migrated electrophoretically with the alpha-globulin fraction of the serum proteins. Pre-exposure of the rat hemidiaphragm to insulin or antagonist serum did not abolish the inhibition. The factor is not a lipoprotein and is inactivated by heating to 100° C for four minutes. It does not compete with insulin for binding sites on the diaphragm, nor does it prevent the binding of insulin by the diaphragm. It is devoid of insulinase activity.

It is postulated that the antagonist is bound rapidly and firmly to the diaphragm independent of insulin and then interacts with insulin to abolish its effect.

SUMMARIO IN INTERLINGUA

Observationes in Re le Natura del Antagonista Humoral a Insulina, Que Es Associate Con Acidosis Diabetic

Le antagonista seral a insulina que occurre in acidosis diabetic es describite plus detaliatemente. Il pare que illo non es relationate al secretion de hormon de crescentia. In duo del casos studiate, le antagonista non esseva demonstrabile in le sero sex a nove horas post le initiation del therapia a insulina. Le activitate del antagonista non esseva dialysabile e migrava electrophoreticamente con le fraction globulina alpha del proteinas seral. Pre-exposition del hemidiaphragma del ratto a insulina o a sero con antagonista non aboliva le effecto inhibitori. Le factor in question non es un lipoproteina; illo es inactivate per calefaction a 100 C durante quatro minutas. Illo non rivalisa con insulina in le occupation de sitos ligatori super le diaphragma e non preveni le ligation de insulina per le diaphragma. Illo possede nulle activitate de insulinase.

Es postulate que le antagonista es ligate rapidemente e firmemente al diaphragma sin dependentia de insulina e que postea illo interage con insulina, aboliente su effecto.

ACKNOWLEDGMENT

We are indebted to Dr. Harry Saroff of this Institute for performing these electrophoretic separations of the protein fraction.

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DISCUSSION

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): The presentations by Dr. Colwell and Dr. Field provide a valuable up-to-date summary of the two principal components of insulin antagonism or insulin resistance, using those words in the broad sense. There certainly are immunologic forms of insulin resistance. Dr. Colwell and his discussers made that quite clear.

There is certainly some form of physiological or other antagonism, as Dr. Field brought out so well. Dr. Field demonstrated two things which should be correlated with what Dr. Colwell said, and I try to do so in this fashion. Dr. Field showed that two patients who had never been treated with insulin had insulin inhibitor. They had not developed antibodies to any exogenous product. Secondly, he showed that this inhibitor was no longer present after recovery from acidosis, a matter of hours, and most antibodies don't disappear that fast. Since I am not an immunologist, this is subject to correction.

There is one more thing. I think that Dr. Field said that he thought the pituitary and adrenal cortex did not have anything to do with this.

JAMES B. FIELD, M.D.: They weren't the main factors responsible for it.

DR. LUKENS: One of the difficulties is that these studies are insulin assays, whether the operated mouse or the rat diaphragm is used. They are not the direct chemical measurement of insulin. Now, an assay measures effective insulin, and effective insulin may be a trace of insulin with no inhibitor or it may be an enormous amount of insulin still with some inhibitor. That makes it difficult to differentiate as to what is happening at certain times. Dr. Vallance-Owen has worked with animals in which these glands have been removed. He finds the depancreatized animal has zero insulin by his method and considerable inhibitor. A Houssay animal (minus the pancreas and pituitary) has zero insulin and no inhibitor, so I think we must keep an open mind as to what any endocrine gland is doing. In addition the methods of assay have differed in different laboratories.

Thus, in Dr. Colwell's work, mice were used for assay. In Dr. Field's work glycogen deposition in the rat diaphragm was used, whereas Dr. Vallance-Owen is using the uptake of glucose from the medium by the rat diaphragm.

These technical differences must be resolved and understood before final interpretation is made, but I would like to congratulate both of these workers on a really marvelous presentation.

ROBERT WM. WEIGER, M.D., (*Chicago*): I would like to compliment Dr. Field on an excellent piece of work, and to ask a question prefaced by a comment.

P. G. Scheurlen in Germany has reported that in severe and untreated diabetes, he has observed an elevation of the alpha-2 globulin returned to normal after corrective treatment with insulin. This abnormal elevation was demonstrated electrophoretically by Scheurlen.

What were the alpha globulin contents of your patients' sera during the insulin resistant phases? Were there any quantitative changes in the alpha globulin contents of the sera after the patients had gone from the resistant to the nonresistant phase?

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): I am sure that the workers doing the fundamental work would agree we shouldn't give up any simple clinical means of studying the return of sensitivity to insulin in patients in diabetic coma, until they have a better method available for clinical work.

Dr. Field stressed that there was no correlation of the antagonist with CO_2 combining power and the *p*H of the blood. He didn't mention whether or not there was any correlation with the degree of ketonemia, however. If I understood the slides correctly, there were two patients in diabetic coma who presented no antagonists in the serum. If these cases were in diabetic coma, then a study of the decreasing degree of ketonemia would be

a reliable means of detecting the return to sensitivity to insulin in patients who have no antagonist.

I would like to ask Dr. Field if he has had an opportunity in this splendid work of his to study a parallel between the antagonist and the degree of ketonemia because in my experience as the ketonemia subsides in the treatment for diabetic coma, insulin sensitivity returns without fail.

GEORGE M. GUEST, M.D., (*Cincinnati*): I, too, should like to pay compliments to this beautiful piece of work. Since Dr. Field mentioned the studies that Dr. Mackler and I reported on the inhibiting effects of acidosis on insulin action, I should like to elaborate this point.

As explained in our reports, we employed ammonium chloride infusions in normal dogs to produce acidosis in order to study the effect of acidosis, per se, apart from other factors of ketonemic acidosis in diabetic subjects. The results indicated that low *p*H is a critical factor inhibiting the blood-sugar lowering effect of insulin and at the same time inhibiting the decreases of potassium and inorganic phosphorus in the blood that normally accompany the fall of blood sugar after insulin. It should be noted also that immediately after acidosis was corrected by sodium bicarbonate these dogs responded normally to test doses of insulin, showing that the acidotic state left no lasting inhibitory after-effect on insulin action. Thus, it must be borne in mind that the effect of acidosis, low *p*H of the blood, in inhibiting insulin action, is only one of many factors in the metabolic derangements that may lead to insulin resistance in the patient with diabetic coma. Ketonemia, stressed by Dr. Duncan, is closely correlated with the severity of acidosis in diabetic coma, another one of many closely interrelated factors in the vicious circle of mutually aggravating disturbances.

RACHMIEL LEVINE, M.D., (*Chicago*): I was much interested in this presentation and the one preceding it, since they begin to throw light on the various phases of insulin antagonism and resistance. It struck me that the two patients mentioned by Dr. Field, who despite acidosis did not show insulin resistance, were just the patients who had high corticosteroid levels in their blood; as if they were spontaneously treated with ACTH.

I wonder whether the common denominator is the outpouring by the liver, under certain conditions, of many species of proteins. In one case, alpha globulins, containing a factor which combines with insulin; in another case gamma globulins, which are immunologically related to insulin. It may be that ACTH and the steroids nonspecifically depress the production and release of all such protein fractions.

Have you done any studies on the corticosteroid level of patients who did show the insulin antagonist, as contrasted with those who didn't? Since your factor is not trypsin-sensitive and is attached to the alpha globulins, is there any possibility that it is allied to the protamines since these substances are good "binders" of insulin?

DR. FIELD: I would like to thank the discussers for their discussions. In regard to Dr. Weiger's question, we have not measured any alpha 1 or alpha 2 globulin levels in patients during diabetic acidosis so we have no information other than the report by Scheurlen (Scheurlen, P. G. Serum protein changes in diabetes mellitus. Klin. Wchnschr. *33*:198-205, March 1, 1955) from Germany, that these protein fractions are elevated.

In regard to Dr. Duncan's question, we have had only one occasion to attempt to correlate the degree of ketonemia and insulin resistance. In this patient there was a good correlation.

We are hopefully waiting for Dr. Duncan to supply us with some specimens in which he has done the qualitative acetone test without telling us the results, and then we can do our assay, and then see if there is any correlation or not. But it certainly might be that this would be an excellent way of telling when a patient first is admitted as to whether or not large doses of insulin will be required.

In answer to Dr. Levine's question, we have not measured the steroid levels in the patients who have insulin antagonist.

One of the difficulties in this problem has been procuring enough serum to test for antagonist, and if there is antagonist, to have enough serum left to do other studies. So far we have not felt we could spare the amount of serum necessary for measuring blood steroids. However, if we do have the occasion where we have enough serum from a patient, I think that would be a very worth-while thing to do.

The possibility of this being protamine or some other substance that binds insulin certainly exists. The fact that the antagonist does not prevent insulin from being bound to the tissue, and the antagonist also is effective whether the diaphragm is exposed to it or insulin first would tend to indicate if there is any binding, it is within the diaphragm itself rather than in the medium before the diaphragm is exposed to insulin.

The Development of Diabetic Retinopathy

Effects of Duration and Control of Diabetes

Robert C. Hardin, M.D., Robert L. Jackson, M.D.,†*
Theodore L. Johnston, M.D.,‡ and Helen G. Kelly, M.S.,§ Iowa City

Evolution in the treatment of diabetes mellitus has been marked by a succession of problems brought to notice by newly acquired knowledge or by change in the course of the disease resulting from better therapy. For example, improved treatment has brought longer life to diabetic patients, but in the second and third decades of their disease they often become subject to degenerative vascular lesions. Determination of the exact nature of these lesions is one of the important problems of the present. The fundamental question is whether the degenerative diseases which accompany diabetes are a part of its natural history or whether they are complications. If the first viewpoint is proved correct, the diabetic patient must be regarded as facing the inexorable course of an unalterable disease. Contrariwise, if the other concept is the true one, degenerations, when the pathologic physiology of their production is understood, should be preventable.

It has been recognized for many years that diabetics are prone to develop vascular disease at an early age and at a rate exceeding that of persons without diabetes. The arteriosclerosis and atherosclerosis which are part of this process differ not at all from those seen in nondiabetic individuals except in certain clinical features. Although both are of interest to the student of diabetes and of utmost importance to the patient, there are other degenerative lesions which lend themselves more readily to investigation. Among these is diabetic retinopathy which begins as a visible capillary micro-aneurysm. This lesion, which occurs in the renal glomerulus and is suspected of being present in other places, may be regarded as peculiar to diabetes. From the standpoint of the investigator it is well adapted for study. Other lesions might be chosen such as the diabetic cataract, intercapillary glomerulosclerosis or polyneuritis, but the first of these occurs with relative infrequency and may regress even after a considerable period; and the others are difficult to diagnose accurately in the early stages or may be confused with similar diseases. The retina is easily examined and the progression of retinopathy has been well established. For these reasons we have chosen retinopathy as an index of the presence and degree of degenerative disease. Our studies have been concerned with factors which might influence its development. Our subjects are a group of juvenile diabetics who have been followed in the clinics of the University Hospitals for periods from ten to thirty years.

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COMPOSITION OF THE GROUP

Patients are accepted into the study group when they enter the second decade of diabetes. The course of their disease from its onset is a matter of written record. The group now numbers 132 of whom 69 are men and 63 are women. Periodic visits to the clinic afford the opportunity to examine each patient carefully, to evaluate the control of the diabetes in the interval since the last visit and to make laboratory observations.

The data to be presented here are for the most part limited to the period ending September 1954. At that time the median age of the group was 24.3 years. Figure 1 shows the age distribution of the group.

All are juvenile diabetics who developed their disease before the age of fifteen years except three who became diabetic in their sixteenth year and one whose first symptoms appeared just after his nineteenth birthday. The earliest onset in the group was at the age of six months. Figure 2 shows the number who developed diabetes in

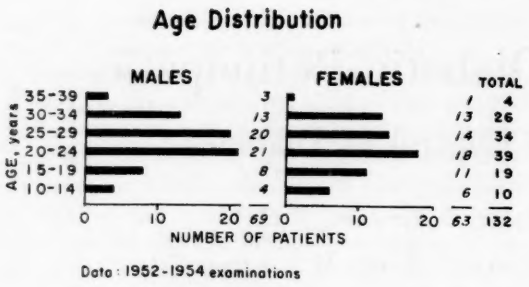

FIGURE 1

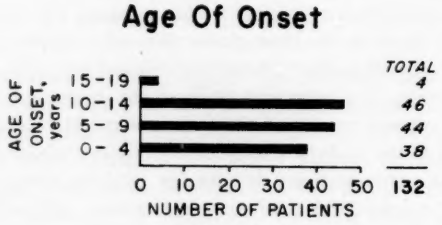

FIGURE 2

each of four age periods of five years. All, as is generally true in juvenile diabetes, have a moderately severe to severe form of the disease as indicated by insulin dosage and insulin-weight ratios before attaining adulthood.

The plan of treatment in all had as its goal the achievement of normal growth and development and exact control of diabetes. To this end diets were designed to insure proper growth. These were complete in all respects.[1] As the patients matured diets were changed to fit adult requirements, energy demands and work schedules. Total dosage and distribution of insulin were ordered with the intent of bringing about excellent control as measured by normal blood sugar levels, freedom from glycosuria, absence of hypoglycemia and avoidance of ketosis at all times. Not all patients achieved this goal constantly but, in striving for it, many have attained a very good degree of control for many years. Some, however, have fallen short and, although we regard this as a joint failure, it does afford the opportunity to make certain comparisons.

PREVIOUS STUDY

In 1949 we reported upon a group of seventy-five diabetic patients who had had their disease for more than ten years.[2] All were juvenile diabetics and their characteristics and the objectives of their treatment were those described for the present group. In fact, the majority are included in the present study. Our conclusions at that time were that, so far as retinopathy is concerned, its occurrence and severity are not related to sex, severity of the diabetes nor age of the patient at onset. Two factors seemed to influence the appearance and progression of the retinal lesions and these were the duration of diabetes and the degree of control achieved. When these were tested, statistically significant degrees of correlation were found in both instances. The value for the relationship between duration of diabetes and the presence of retinopathy was significant at the 1 per cent level of confidence and that for the relationship of the degree of control to retinopathy was significant beyond the 1 per cent level. From this could be concluded only that both factors were of importance in the development of retinopathy.

The question of the relative importance of the two could not be settled. It was known that the average time required after the onset of diabetes for retinopathy to appear is thirteen years.[3] The median duration of diabetes in the group was 15.2 years which was close to the average time required for the development of retinopathy. It was obvious that this study would have to be continued in order that, as time passed, the influence of the period required for retinopathy to appear could be eliminated. In this way the true relation of duration of diabetes to development of degenerative disease might become evident. At the same time a re-evaluation of the influence of control could be made. A clear distinction between the relative importance of these two factors could help answer the fundamental question of whether degenerative disease is a part of the natural history of diabetes or a potentially preventable complication.

With this objective the study was continued. Those persons who had been subjects previously were followed and others were added to the group as they passed into the second decade of their disease in order that more valid comparisons could be achieved not only by study of the former subjects over a longer period but by increasing the number of observations.

METHOD

For the purpose of statistical analysis it was necessary to group our observations into classes. There were three items which had to be so treated. The first of these was duration of diabetes which was calculated to the nearest year. Thus the value of 16 was taken for the duration of disease in all patients whose onset of diabetes had been from 15 years and 6 months to 16 years and 5 months before their last examination. The presence and degree of retinopathy were depicted by a scale ranging from zero to nine in which zero denotes a normal retina and nine proliferative retinopathy. Descriptions of the various stages are given as follows.

CLASSIFICATION OF RETINOPATHY

0—normal.

1—venous dilatation.

2—few punctate hemorrhages and/or capillary aneurysms.

3—many punctate hemorrhages and/or capillary aneurysms.

4—early central punctate retinopathy.

5—advanced central punctate retinopathy.

6—central punctate retinopathy plus pre- or subretinal bleeding.

7—central punctate retinopathy plus cotton-wool patches.

8—mixed diabetic and hypertensive retinopathy.

9—proliferative retinopathy.

To designate the degree of control of diabetes achieved over the entire duration of disease the over-all control rating was computed. This is derived from the interval control rating which is a number designating a certain degree of control. An interval control rating was assigned at each evaluation of the patient to describe the degree of control achieved since the last examination. The over-all control rating is the sum of the products of the interval control ratings and the number of years over which each obtained. The scale of interval control ratings and an illustration of the computation of the over-all control rating are given below.

Interval Control Rating:

0—Freedom from sugar in the urine except for occasional slight traces. Approximately normal blood sugars. (good)

½—Fluctuating from rating 0 to 1.

1—Less than one-half the urine specimens free from sugar and small amounts of sugar in the remainder. Slightly elevated blood sugars. (fair)

2—Fluctuating from rating 1 to 3.

3—Varying amounts of glycosuria constantly. Elevated blood sugar levels. (poor)

4—Continuous gross glycosuria. Elevated blood sugar levels. (very poor)

Computation of Over-all Control Rating:

Seven years with rating 0 = 0
Eight years with rating 1 = 8
Four years with rating 3 = 12

Over-all Control Rating = 20

After tabulation of the data in this fashion scattergrams were constructed by plotting the degree of retinopathy against either duration expressed in years or against degree of control as expressed by the over-all control rating. Analysis of these graphs by the method of Pearson gave the relationship between the two items being tested expressed as the coefficient of correlation.

RESULTS

First to be considered was the original group of 75 patients studied in 1948 and reported upon in 1949. In our previous publication[2] the correlations were done by the chi square method and, for purpose of comparison, it was necessary to calculate the coefficient of correlation by the method chosen for the present investigation. When this was done with the data collected in the period ending in 1948 good correlation was found, as before, between degree of control and retinopathy and between duration of diabetes and retinopathy. The ***r*** value for the relation between control and retinopathy was 0.749 which is significant beyond the 1 per cent level of confidence. That for the relation between duration and retinopathy was 0.334 which is significant at the 1 per cent level. This bore out the conclusion previously reached that both duration of diabetes and degree of control influenced the appearance and severity of retinopathy although the latter was of somewhat more significance. The scattergrams on which these calculations are based are shown in figure 3.

It was desired to study these patients again at a later date and for that purpose the evaluation period of March 1, 1952, to Sept. 1, 1954, was chosen for the collection of data. During that time 66 of the original 75 patients returned for examination. In that interval two died of renal failure (intercapillary glomerulosclerosis) at the ages of 31 and 33 years and with a duration of diabetes of 21 and 22 years respectively. These two patients were included in the series. Another who died at home shortly after his last examination of cause unknown to us was included also. Two patients were excluded from the series because at the last examination they had a duration of diabetes slightly less than fifteen years. One had retinopathy and one did not. There were, then, paired data available for 64 of the original 75 patients.

All had a duration of diabetes exceeding 15 years with a range of 15 to 29 years. The median duration for the group was 21 years which is well above the 13 years known to be the average time required for the development of retinopathy. When the data from these examinations were analyzed by the methods described above it was found that the presence and severity of retinopathy still correlated inversely with the degree of control of diabetes. The coefficient of correlation was 0.651 which is significant beyond the 1 per cent level of confidence. However, no correlation could be found between retinopathy and the duration of diabetes. The ***r*** value was 0.171

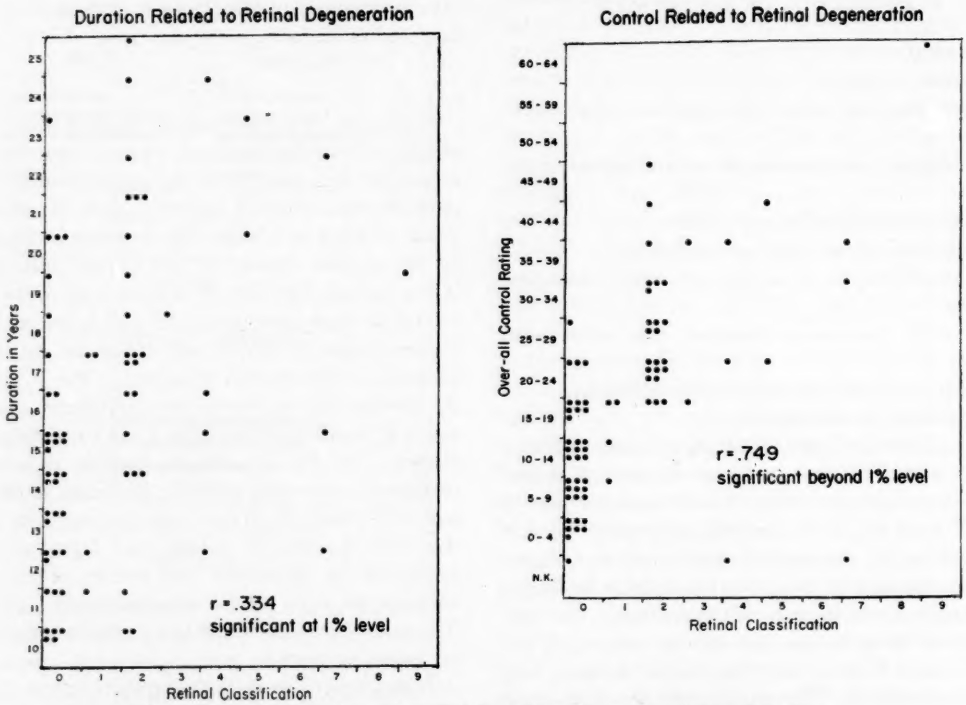

FIG. 3. Relation of duration and control to retinopathy in 75 patients—1948 study.

which is not significant. Thus, in the same group of patients the passing of an average of five years eliminated duration of disease as a factor in the development of retinopathy. The scattergrams for this analysis are shown in figure 4.

The data collected for the entire group of 132 patients (including the 66 from the previous study) were then analyzed in the same manner. The use of a larger number of subjects offered the opportunity to test the validity of the analyses performed for the smaller series. Reliable paired data were available for 123 patients. The correlation between degree of control and retinopathy was found to be good. The *r* value was 0.661 which is significant beyond the 1 per cent level. The coefficient of correlation between duration and the development of retinopathy was 0.318 which is significant at the 1 per cent level of confidence. It must be noted that the duration of diabetes in this group ranged from 10 to 29 years with a median of 16.5 years. The scattergram for this group is shown in figure 5.

Finally a scattergram was constructed in which the presence and degree of retinopathy were plotted against the duration of diabetes at the time of the last examination of each patient who had been studied at any time in the period between March 1948 and December 1955 inclusive. This was done in order to include those patients who had disappeared from the series through failure to return or, more particularly, through death from complications of diabetes, and who had been excluded from the previous analyses. In this final group there were 140 subjects who had a duration of diabetes of more than 10 years and for whom there were paired data. In 93 instances the duration of disease exceeded 15 years. When the correlation between duration and the presence of retinopathy was studied for the entire group it was found to be good. The *r* value was 0.270 which is significant beyond the 1 per cent level. However, when a similar analysis was done for those patients who had passed the fifteenth year of their diabetes at the time of the last examination the results were entirely different. The coefficient of correlation was 0.079 which is not significant. It should be mentioned that, of the four who are known to have died, three are included in the group above fifteen years' duration. Figure 6 shows these relationships.

INCIDENCE OF RETINOPATHY

The incidence of the various stages of retinopathy in

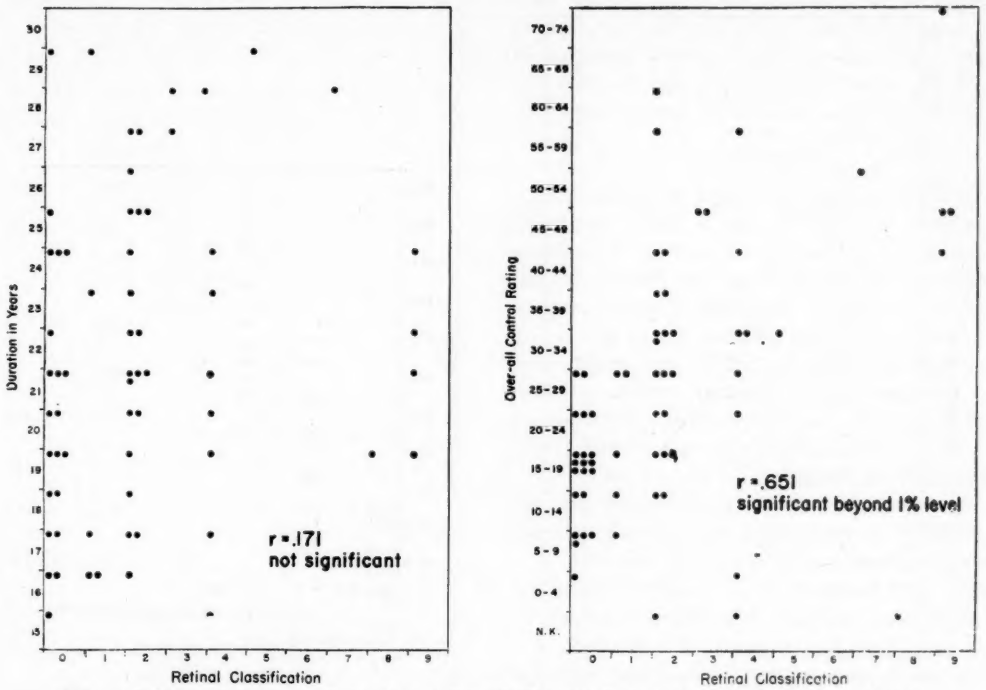

FIG. 4. Relation of duration and control to retinopathy five years later in 64 of the original 75 patients.

140 patients at the time of their last examination is shown below. The duration of diabetes in this group ranged from 10 to 29 years.

Normal Retinae	54	38.5 per cent
Dilated veins only	14	10.0 per cent
Micro-aneurysms only	48	34.3 per cent
Advanced Retinopathy	24	17.1 per cent

It has been our practice to regard venous dilatation as the first stage of diabetic retinopathy. However, if the usual criterion, the appearance of the capillary micro-aneurysm, is accepted 48.5 per cent of this series had normal retinae.

DISCUSSION

The question of whether retinopathy and other degenerative disease accompanying diabetes may be prevented or delayed by properly ordered treatment has been the subject of much investigation without a universally accepted decision. Probably the answer will not be achieved until the pathologic physiology of degenerative lesions is completely understood and causative factors are clearly related to their effects. In the meantime one must treat diabetic patients and choose between the two viewpoints concerning the nature of degenerative disease. One is that diabetics must inevitably develop degenerations for they are a natural part of diabetes. The other is that they are complications which may be prevented. Reports of investigators offer varying conclusions.[4, 5, 6, 7] A series of papers from the Joslin Clinic emphasize that good control is of utmost importance in the prevention of degenerative vascular lesions. Others hold the same opinion. The opposite viewpoint has also been presented by many in reports such as that of Larsson[7] and others. They concluded from a study of 257 juvenile diabetic patients that increased incidence of vascular lesions did not follow degrees of control lesser than those advocated by others. They did emphasize that diabetic patients must be closely supervised. A review by Engleson[8] summarizes the literature up to 1954 and offers the conclusion that there is better evidence for more exact control than there is against it.

Our present study was designed to separate, if possible, the influences of duration and degree of control on the development of diabetic retinopathy. The subjects were grouped in four different ways but, no matter what division was made, there always existed a highly significant correlation between degree of control and the incidence and severity of retinopathy. Patients with good control had a much lower incidence of retinopathy than those with lesser degrees of control and retinal lesions

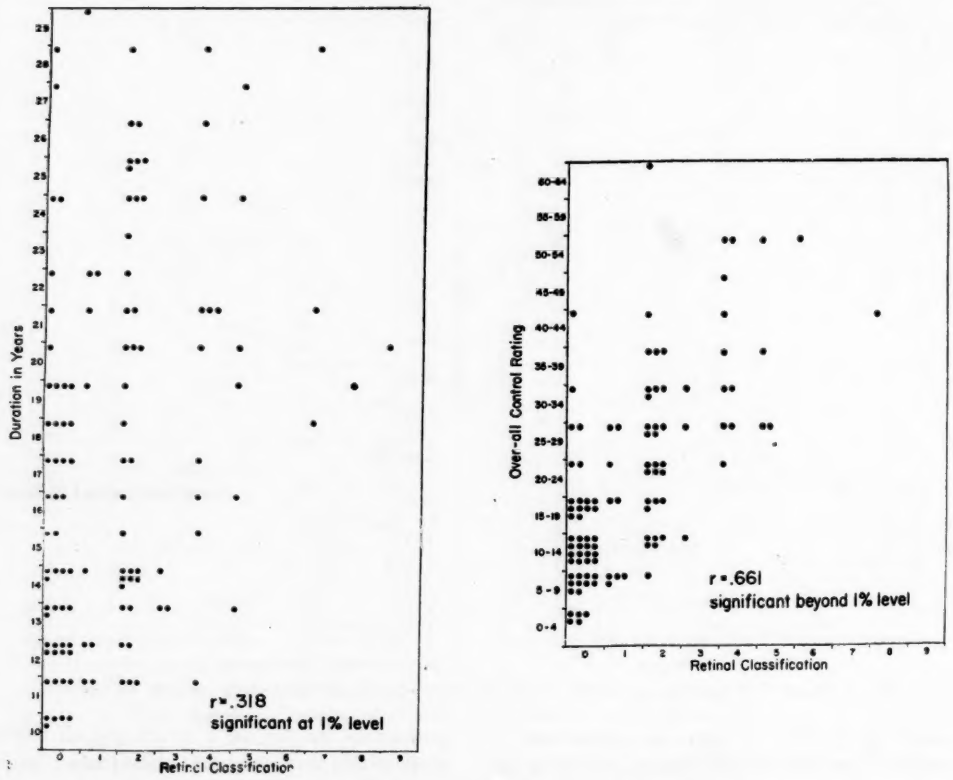

FIG. 5. Relation of duration and control to retinopathy in 123 patients—1954 study.

tended to be more severe in those with poorer control.

The influence of duration also was investigated in the four groupings of patients. In our original study[2] duration of diabetes correlated well with the incidence of retinopathy. Recalculation of that data by our present method confirmed this observation. However, when these same subjects were observed an average of five years later, there was no demonstrable relationship between duration of diabetes and the incidence and severity of retinopathy. This was striking because, if retinopathy were an inevitable concomitant of diabetes, it should have been observed with greater frequency and severity as the duration of the disease increased. Observation of exactly the opposite argues against duration of diabetes being a strong influence in the production of degenerative disease and against vascular disease being a part of the natural course of diabetes. A possible explanation of why this was not evident previously is found in the fact that retinopathy, when it occurs, appears on the average thirteen years after the onset of diabetes. In our 1948 study the median duration of diabetes was 15.2 years so that statistical analysis might have reflected the time required for retinopathy to develop rather than the true influence of duration on its incidence. At the time of the second study of this group the median duration of diabetes was twenty-one years which possibly eliminated the factor of the time required for retinopathy to appear.

Analysis of the data from 123 of the larger series of 132 patients with a median duration of their disease of 16.5 years gave a correlation coefficient between duration and retinopathy significant at the 1 per cent level of confidence. This was similar to that found in the original study. Finally all patients were grouped according to their duration of diabetes at the time of their last examination. The relation between duration and incidence and severity of retinopathy was determined for all 140 patients and again for only those whose diabetes had been present for more than 15 years. In the first instance the correlation coefficient was 0.270 which is highly sig-

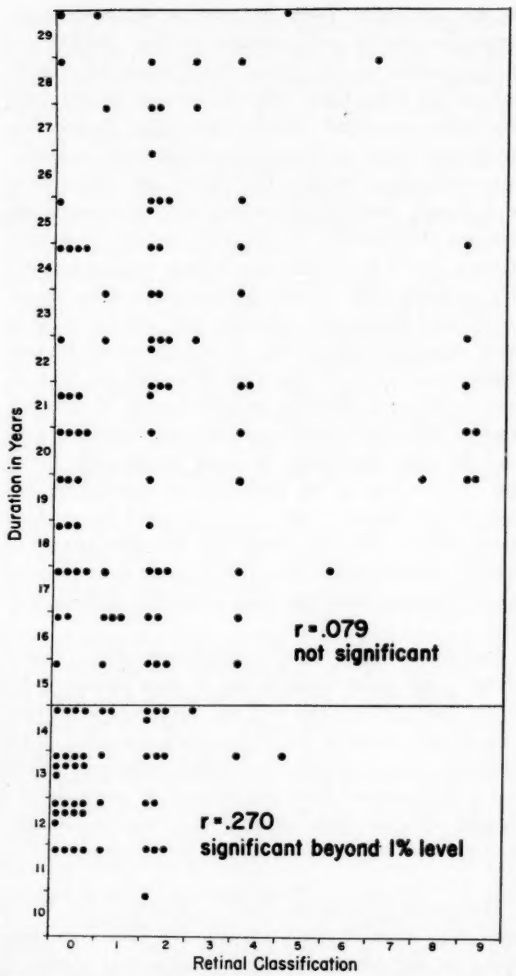

FIG. 6. Relation of duration and control to retinopathy in 140 patients—last examination.

nificant. When the 93 subjects whose duration exceeded 15 years were similarly tested the correlation coefficient was 0.079 which is of no significance. This demonstrated again that study of a group of diabetics whose mean duration of disease significantly surpasses the required time for the development of retinopathy fails to show any relationship between duration and retinopathy.

Thus, except for the time required for it to appear, the only constantly identifiable factor in the development of retinopathy is the degree of control of the diabetes. This is an observation concerning the conditions under which retinopathy occurs and not an explanation of the mechanism of its production. Elucidation of this must await a better understanding of the pathologic physiology of diabetes and of vascular disease. It may be suggested, however, that observable differences in the physiology of well controlled and poorly controlled diabetics may provide information useful in this respect.

SUMMARY

Observations on a group of 140 juvenile diabetic patients with a range of their disease from 10 to 29 years have been made. The data were analyzed for the relationship of duration and control to the development of retinopathy. Highly significant correlations between degree of control and incidence and severity of retinopathy were demonstrated. When groups of patients whose duration of diabetes exceeded fifteen years were studied no correlation between duration and retinopathy was found. From this it was concluded that:

1. Except for the time required for its appearance (average thirteen years) duration of diabetes is not an important factor in the development of retinopathy.

2. The only identifiable factor bearing a constantly significant relationship to the incidence and severity of retinopathy is the degree of control of the diabetes.

3. Differences in the pathologic physiology of well controlled and poorly controlled diabetic patients may provide information useful in the explanation of vascular degeneration.

SUMMARIO IN INTERLINGUA

Le Importantia Relative de Duration e Controlo in le Disveloppamento de Retinopathia Diabetic

Esseva observate un gruppo de 140 patientes diabetic juvenil in qui le duration del morbo esseva inter 10 e 29 annos. Le datos esseva analysate pro determinar le relation inter duration e controlo e le disveloppamento de retinopathia. Esseva demonstrate correlationes multo significative inter grado de controlo e frequentia e le severitate del retinopathia. Nulle correlation inter duration e retinopathia esseva trovate in le studio de gruppos de patientes in qui le duration de diabete excedeva dececinque annos. Ab iste factos nos concludeva que:

1. Con le exception del tempore requirite pro su apparition (dece-tres annos al media), le duration de diabete non es un factor importante in le disveloppamento de retinopathia.

2. Le sol factor identificabile que ha un relation constantemente significative con le frequentia e severitate de retinopathia es le grado de controlo del diabete.

3. Differentias in le physiologia de patientes diabetic sub bon controlo e mal controlo pote provider informationes utile in le explication de degeneration vascular.

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DISCUSSION

HENRY DOLGER, M.D., (*New York City*): I am amazed at the contrast in these two papers. The last one is probably the most adynamic view of the subject I have ever heard. In contrast, Dr. White presents the most ideal, dynamic attitude towards diabetes. If one is to limit the objective criteria of vascular damage just to retinopathy, it is true that in thirteen years one will see just various graduations of degenerative change. But it is obvious to all of us here, as Dr. White has shown, that it's first retinopathy, then arterial renal lesion, and thirdly generalized vascular disease.

I go back to Dr. White's paper of ten years ago. Her report at that time indicated that 94 per cent of the juvenile patients had vascular damage. Ten years later, today, with what she calls better control, the results are still 94 per cent; so where are we ten years after better control?

GEORGE M. GUEST, M.D., (*Cincinnati, Ohio*): In studies of the sort reported by Dr. White earlier and now by Dr. Hardin, I should like to suggest that more attention should be paid to the exceptional cases among the large groups of patients classified according to the authors' standards as "well-controlled" and "poorly controlled." The figures on the incidence of complications, higher among the poorly controlled groups than among the well-controlled groups are of course impressive; but let us bear in mind that within both groups there are notable individual exceptions. Individual behavior cannot be prophesied from statistics on group behavior. Among presumably well-controlled patients complications of degenerative organic disease do sometimes occur early; and, on the other hand, some notoriously undisciplined and badly controlled patients have gone longer than thirty years with no discernible degenerative cardiovascular-renal-ocular lesions. The individuals within these large groups, however subdivided, have in common one principal characteristic, namely, the diagnosis of diabetes mellitus. Apart from that item in their medical histories they probably differ among themselves in their physiological and biochemical patterns and genetic traits as much as do a similar number of individuals in the nondiabetic population. Recognition of exceptions, with regard to the development or nondevelopment of complications in individual diabetic patients emphasizes our great need for more knowledge of many fundamental factors that are involved in the pathology of concomitant features of the disease. There is a great need for study of genetic factors that may determine the development of chronic cardiovascular-renal-ocular disease apart from the genetic trait or traits that may determine diabetes mellitus.

JOSEPH L. IZZO, M.D., (*Rochester, New York*): There is one point I would like to have cleared. I was in the back of the room and was unable to get a close look at the charts. I would like to know what is the magnitude of your positive correlation coefficients? Those that were positive, how highly positive were they? I thought some of them, although they were significantly positive were of very low order, some around 0.2 or 0.3.

ELIZABETH F. TULLER, PH.D., (*Boston*): Dr. White mentioned some of the work that Dr. Ditzel has been doing in our laboratories with conjunctival studies as another way of investigating vascular changes in diabetes. (DIABETES 3:99-106, 4:474-76.) These studies may also be useful in the problem of the relationship of duration to vascular lesions as well as to control. It thus might be well to point out two items, one from his work and one from our protein studies.

The conjunctival changes which form characteristic patterns in the diabetic are found very early. In fact, in some cases glucose tolerance studies were done simultaneously with the conjunctival work, and Dr. Ditzel's description of vascular changes similar to those found in well-established diabetes coincided with the discovery of the borderline or prediabetic, indicating that there was some type of vascular change going on very early in the disease. Thus the question might be raised as to whether these changes are a genetic-related factor and

parallel the clinical course of diabetes mellitus. Certainly some of the recent work that he has done has indicated that these vascular changes may have increased in degree of severity as the clinical symptoms of retinopathy have appeared.

Also we have found that in diabetics with poor control, and with no evidence of vascular changes in the retina and the kidney, the serum protein patterns were similar to those of the diabetics with newly indicated clinical symptoms of vascular changes, even though the duration of the disease was less in the former group. The observation has been that protein changes follow both increased duration and poor control. However, in a group with good control, the longer the duration of the disease, the closer the serum protein pattern came to that abnormal pattern found in the diabetic with observable clinical changes of vascular lesions in the retina and the kidney.

This leads one to go along with Dr. Guest's idea as to the need for time and for study to gain an understanding of some of the background of this type of material.

ARNOLD LAZAROW, M.D., PH.D., (*Minneapolis*): In interpreting the data presented it is important to ascertain whether the poor control of the diabetes results from lack of patient cooperation or whether it is the result of the diabetic state, per se. If one were to assume that an unknown etiologic factor acts in two ways (1) it makes the diabetes more difficult to control, (2) it accelerates the development of the complications of diabetes, then in grouping the poorly controlled diabetics one would be selecting those individuals who are prone to develop the complications of diabetes. Do you have any specific information in the group of patients studied as to whether the poor control is a characteristic of the diabetic state, or whether it is due to lack of patient cooperation?

PRISCILLA WHITE, M.D., (*Boston*): I don't think I have expressed myself clearly. I think that right now our present tools, mixtures of insulin, regular and intermediate, in split doses, will give the next generation of diabetics a better chance for better chemical control than this group which I reported today.

ROBERT C. HARDIN, M.D., (*Iowa City, Iowa*): I think Dr. White has partially answered Dr. Dolger. I am not quite in agreement with Dr. Dolger, that this is an adynamic approach to diabetes. Perhaps we need a definition.

As I said, this paper described the people in whom degenerations appear, but does not say why they appear. Certainly one would not stop here but would go on to find out as much more as possible. Many who have spoken on this program have demonstrated this approach to the study of the production of degenerative lesions. It may be some of our observations when classified into those from controlled and those from uncontrolled diabetics will show differences of importance in the elucidation of this problem.

Dr. Guest, I think, talked on that very important subject, and I agree wholeheartedly with him. The people in this group who interest me most are those of whom he spoke, those who should have degenerative disease but do not, and those who shouldn't but do, and we have both.

These persons are of extreme interest, and we are carrying out studies on them.

Dr. Izzo asked about the degrees of correlation or rather the orders. I am sorry if they could not be seen at the back of the room. Those for duration were always of a lower order of magnitude. In the 1948 studies the values were 0.33 for duration and 0.74 for control. For the study of these people five years later, they were 0.17 for duration and 0.65 for control. In the next study the values were 0.31 for duration and 0.66 for control. The last study did not include control, but was for duration only. The values were 0.27 for the entire group and 0.07 for those above fifteen years.

Dr. Lazarow has brought up the question, I think, of whether there are two kinds of diabetes or more. Is there a kind of diabetes which is easily controlled, and which in its natural history does not go on to degenerative disease, and is there another which cannot be controlled, and which in natural history goes on to degeneration? The studies which we presented today do not answer this question. These were homogenous groups of patients and all were juvenile diabetics.

EDITORIALS

THE INFLUENCE OF THE PATIENT'S BEHAVIOR AND HIS REACTION TO HIS LIFE SITUATION UPON THE COURSE OF DIABETES

Although we have learned a great deal about the metabolic defect in diabetes, and understand much about its pathogenesis, we still lack a definitive knowledge of the etiology of the syndrome, and we are unable to "cure" it in the sense we can cure pneumococcus pneumonia or acute appendicitis. We are forced to "manage" the disease by controlling its manifestations in so far as this is possible. Such control is dependent upon the control of the factors which influence the manifestations of the disorder. The variables which are generally recognized as pertinent to its clinical management, and which we know must be controlled in order to control its manifestations, fall into only a few general categories. They may be listed as (1) dietary intake, (2) insulin dosage, (3) physical activity, (4) intercurrent disease, and (5) the behavior of the patient and his relation to his life situation. The last group of variables, which are the most difficult to control, are often those which are least understood by the physician, and which receive the smallest part of his consideration.

We do not yet know whether there are any personality features which are inextricably linked with diabetes. There may well be none. But, for whatever reason, certain types of behavior are often seen among patients with diabetes; and they may immensely complicate therapy. Perhaps the most common of these is an unusual need to eat. Hyperphagia is a cardinal symptom of diabetes. Often it is based upon an insistent craving for food, which becomes more intense during periods of loneliness, boredom, tension, and dejection. It may long precede the appearance of hyperglycemia and glycosuria, and it is not always abolished by treatment with diet and insulin. Because of this craving for food many patients cannot or will not restrict their food intake.

There is some reason to believe that it is common to both obesity and to diabetes, and that it is based upon a quantitative defect in the function of the hunger-satiety mechanism that is controlled by centers in the midbrain. There is also much evidence that the disturbance is particularly great among the pathologically obese, whose lives have been featured by lack of affection and security, and who use food both consciously and unconsciously as a substitute gratification. Whatever its cause, its effect is clear. It makes adherence to diet peculiarly difficult for some people with diabetes—much more difficult than a thin, healthy physician may imagine. It explains much of the laxity, irregularity, willful "cheating" and outright disregard for dietary prescriptions which some patients exhibit.

The person with diabetes, like other humans, requires a balanced diet of adequate caloric content, consumed at regular intervals. The physician need not hesitate to make this clear to his patient. Nor should he pretend that it is a matter of no consequence if his patient eats himself into obesity, or eats so irregularly as to impede the management of his illness. But when patients demonstrate an inability or unwillingness to control their eating, the physician's attitude toward this should be one of dispassionate investigation rather than moral indignation. He will often find it more profitable to attempt to help the patient control his appetite rather than to insist upon a rigid dietary prescription.

Another type of behavior, seen frequently among juvenile and adolescent diabetics, is an alternation between dependent and overdemanding behavior, and explosive rebellion. This behavior pattern usually centers around the mother; but it may also involve a physician or anyone else in a position of parental authority. Those who have studied such patients believe that they feel an intense need for the approval, affection, and protection of the parent, and make excessive demands upon his time and patience in order to obtain these. Eventually the parent reacts with annoyance and rejection, and the patient reacts with hostility and acute rebellion which may include willful disregard of diet, failure to take insulin, disregard of necessary aseptic precautions, and deliberate attempts to precipitate diabetic acidosis.

Because the physician has a long-term, parent-like relationship to his juvenile and adolescent patients, he may find himself involved in a similar cycle with his patient, who makes demands upon his time and patience, who shows need for reassurance and attention, and who at the

same time may be provocative and annoying, deliberately disregarding directions and failing to cooperate with his regimen. Here again, the physician is called upon to exhibit dispassionate concern rather than moral indignation. The problem is that of attempting to understand and control the behavior of the patient in order that his diabetes can be controlled, and this problem is more likely to be solved by an investigation of its causes than by a punitive insistence on a rigid regimen.

Such overt disturbances of appetite and gross behavior provide only a partial explanation of the manner in which the patient's reaction to his life situation may affect the course of his illness. Experimental observations carried out over the past fifteen years have demonstrated that men's reaction to their life situations are associated not only with changes in their mood, thoughts, and gross behavior, but also with direct changes in bodily processes. There is now good reason to believe that any physiological process which can be influenced by the voluntary nervous system, the autonomic nervous system, or the glands of internal secretion, can be altered as men adapt to their social environment. Such adaptations may include changes in energy metabolism and in fluid balance, both of which can have an important effect upon the course of diabetes, even in the absence of any changes in the gross behavior of the patient. Alterations in metabolic patterns may be associated with alterations of circulating glucose and ketone bodies, and evidently with changes in the rate of utilization of glucose in the peripheral tissues; and they may be reflected in changes in the glucose tolerance curve. Likewise, changes in fluid balance during adaptive reactions may be associated with marked alterations in the rate of excretion of water and electrolytes, and of glucose and ketone bodies also. The cumulative effect of such metabolic adaptations, especially when they are superimposed upon the effects produced by rebellious behavior, may be that of precipitating a rapid decompensation of diabetes. Less pronounced metabolic adaptations, occurring over a period of time as the patient adapts to changing demands of his occupation and of his personal life, account for many otherwise unexplained variations in insulin requirement.

The situations to which the diabetic patient responds with metabolic changes appear to have a high degree of specificity for the individual. Thus, it is not uncommon to see a patient occasionally pass through what appear to be major crises in his life with relatively little disturbance in the course of his disease, and later respond to a superficially innocuous event with a major metabolic upheaval. When these events are studied in relation to their pertinence for the patient, often the apparently innocuous situation is found to have been highly threatening to him, while the situation which appeared to be threatening was much less so. By and large, it may be said that the life situations to which patients respond with metabolic changes leading to ketosis are acute conflicts with significant individuals in their lives, usually parents, husbands, wives, or children, or the threatened loss of such a significant person. Situations extending over a period of time and engendering feelings of loneliness, dejection, and chronic resentment are often associated with a relative increase in insulin requirement. These situations also usually center around important members of the family, but sometimes they are related to occupation or finances. Conversely, life situations to which the patient responds with feelings of contentment, security, and relative freedom from care, may be associated with a relative diminution of insulin requirements. Sometimes "excitement," such as experienced during a rapid automobile ride, or during sexual stimulation, may be associated with hypoglycemic reactions.

All of these metabolic fluctuations occur more frequently and to a greater degree in younger and more labile patients, and are especially a feature of so-called "brittle" diabetes. In older, more obese patients, with more stable diabetes, similar metabolic changes can be shown to occur; but their magnitude is relatively smaller, and their influence upon the course of the illness is correspondingly less. When a relatively obese or stable diabetic develops a rapid and marked change in his insulin requirement, this should not be attributed to a metabolic reaction to his life situation except when the situation is a highly potent one, and no other explanation for the decompensation of the diabetes can be found.

The management of diabetes, therefore, is dependent upon the physician's seeing his patient in context. It is not enough to view the person with diabetes simply as a sort of living test tube, in which the proper mixture of diet, insulin, and activity, will always produce the proper degree of regulation, if no other illness is present. It is necessary to view him as a sentient, active member of his society, constantly interrelating with and adapting to his family, his associates, his job, and all of the complex events and situations of the world around him. It is essential to know that his adaptations to his daily life constantly influence the course of his illness. The physician cannot always alter his patient's environment or his reaction to it; but he can at least attempt to understand it. Understanding it, he can take it into account in his management of the illness.

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L. Harry Newburgh

Cecil Striker, M.D., Cincinnati

L. Harry Newburgh was born in Cincinnati and received his early education there. He then went to Harvard, receiving his Bachelor of Arts degree in 1905 and his degree of Doctor of Medicine in 1908. He interned at the Massachusetts General Hospital and then went abroad for one year. Following this he returned to Cincinnati to enter the private practice of medicine. He associated himself with the late Dr. Frederick Forchheimer, who, at that time, was one of the leading internists in the United States. Dr. Forchheimer, among other things, was the editor of Billing's *System of Medicine*. The active practice of medicine did not interest Dr. Newburgh, as he desired to do research work and to enter academic life. He returned to Harvard Medical School in 1911 and taught there for four years. In 1915 he went to the University of Michigan and stayed for thirty-six years, during a greater part of which time he was Professor of Clinical Investigation. He was retired in 1951.

During this very active career he taught thousands of medical students and endeared himself to them through his sympathetic patience and critical evaluation of their ability.

In addition to his teaching responsibilities he was a very active clinical investigator and a prolific writer. He published ninety-six scientific papers and eight monographs either alone or in conjunction with his associates. His first publication appeared in the *Boston Medical and Surgical Journal* in 1916, reporting his investigation on pneumonia. As early as 1919 he became interested in diseases of the kidney and published in the *Archives of Internal Medicine* his first paper entitled "Production of Bright's Disease by Feeding High Protein Diets." He continued his investigation along these lines for many years thereafter, and in 1930, in association with F. H. Lashmet, published an important paper entitled "Specific Gravity of Urine as a Test of Kidney Function." It was only natural that his work on kidney function should lead to subsequent studies on water metabolism and his contribution to this area is well documented in the literature. He was not satisfied with the existing technics of measuring water metabolism and around 1935 he supervised the construction of a remarkable balance scale in a closed chamber. In this apparatus the subject lived for indefinite periods of time during which accurate body water and caloric exchange were measured. This balance scale set a pattern for subsequent metabolic studies.

In 1921 he published a paper in the *Archives of Internal Medicine* entitled "Use of High Fat Diet in Treatment of Diabetes Mellitus." This was an epochal paper in the dietary treatment of diabetes mellitus. He cogently presented the scientific evidence for the validity of use of the high fat, low carbohydrate, low protein diet for the dietary regulation of diabetes. Had it not been for the discovery of insulin at approximately the same time, it probably is safe to say that the principles that he laid down would have been the basis for the dietary regulation of diabetes now. However, with the introduction of insulin, there was no need for such a dietary program. After the discovery of insulin his interest in diabetes waned somewhat and he renewed his interest in kidney diseases and water metabolism, but at the same time made important observations on obesity in particular relationship to glycosuria.

During World War II he spent considerable time at Wright's Field US Army Air Corps, Dayton, Ohio, doing intensive research on the physiology of heat regulation and the science of clothing.

Dr. Newburgh was a great scientist and he, himself, was his severest critic. These characteristics were combined with a warm personality which won him a vast coterie of friends.

He was a member of many scientific societies and among these was the American Diabetes Association. He was a member of the Council from the inception of the Association until 1946. During this period he contributed actively to its affairs. At the Sixteenth Annual Meeting of the American Diabetes Association, on June 9, 1956, he was the recipient of the Banting Medal.

He was born June 17, 1883, and died July 16, 1956, survived by Mrs. Newburgh and his son, Henry.

There are a few of us who worked intimately with him and many who will cherish his memory and I am sure that he has placed his name on the tongue of posterity.

BOOK REVIEWS

THE LIPIDS—THEIR CHEMISTRY AND BIOCHEMISTRY (Volume II). *By Harry J. Deuel, Jr., M.D., Dean, Graduate School, and Professor of Biochemistry, University of Southern California, Los Angeles, California. $25.00, pp. 919, Interscience Publishers, Inc., New York, 1955.*

The chemistry of lipids has been covered in Volume I of this series and the present volume deals with certain aspects of lipid biochemistry. This comprehensive treatise was originally intended to be published in two volumes, but the wealth of biochemical material necessitated expansion to three volumes. Volume II takes up the digestion, absorption, transport, and storage of lipids, and Volume III will include material on their biosynthesis, metabolism, oxidation, and nutritional value. The unfortunate recent death of the author will not interfere with publication of Volume III. According to advice from the publisher, satisfactory arrangements have been made for its completion, and it is scheduled for publication next year.

In these days of well-nigh explosive advances in biochemistry, few are the hardy individuals who have the ability and fortitude to attempt a work of this monumental scope. It is a tribute to the author's standing in the field and to his perseverance that he has succeeded in producing a first-rate monograph which, I believe, will remain a landmark in the lipid field for many years. It is refreshing to find a work of this magnitude, written by one author in a clear, lucid, and informative fashion, instead of the usual collection of separate reviews, each written by a different author. Of especial value to the reader are the numerous descriptions of experimental procedures, and the documentation of data in a large number of tables. The collection and tabulation of data alone must have represented a tremendous task. The inclusion of older, as well as newer material, provides an historical perspective which adds greatly to the value of the subjects covered.

The first section deals with the digestion and absorption of lipids. The first chapter describes the enzymes concerned with the digestion of lipids. This subject is rather broadly interpreted; of the sixty-seven pages devoted to it, thirty-eight pages are taken up with choline esterases and choline acetylase. The role of bile is covered in two chapters. Particularly valuable is the extensive treatment of choleic acid complexes. One of the two chapters on lipid absorption contains a fascinating and informative description of the experimental physiological and surgical procedures used in measurement of lipid absorption.

Of great value to nutritionists is the exhaustive treatment of the digestibility of fats and other lipids. Perhaps of greatest immediate interest to clinicians is the extensive treatment of the subject of blood lipids, covered in eight chapters of 170 pages. Topics of particular current importance are the lipoproteins, and the factors influencing their amounts and types and their relation to atherosclerosis. The interesting and significant effects of the endocrines on blood lipid levels are thoroughly discussed.

The remaining two sections are devoted to the lipid composition of animals as a whole and to specific tissues and their secretions. Especially noteworthy is an extensive discussion of conditions related to fatty liver, to which seventy pages are given, the factors involved and the mechanisms concerned in milk-fat formation, the distribution of lipids in man as a function of endocrine imbalance, and an excellent, though brief discussion of the physiological significance and composition of adipose tissue. Other portions of particular interest to the clinician are the sections devoted to the various lipid storage diseases and to the various obesities.

The printing and binding are of excellent quality and the price of $25.00 is not high by present day standards, considering the size and scope of the work.

MEDICAL PROGRESS, 1956. *Edited by Morris Fishbein, M.D. $5.50, pp. 389, Blakiston Division, McGraw-Hill Book Company, March 1956.*

The 1956 edition of *Medical Progress,* a review of medical advances in 1955, is published by the Blakiston Division of McGraw-Hill Book Company. The editor, Dr. Morris Fishbein, of recognized experience, has selected in this fourth volume of a series of annual publications, an outstandingly competent staff of twenty-nine contributors among whom are included, to name but a few, Elliott P. Joslin, William A. Brams, R. B. H. Gradwhol, Edward S. Judd, Perrin H. Long and Lewis M. Hurxthal. There are twenty-one chapters, mainly on the branches of Internal Medicine but also (and what may make it even more valuable for any physician) including chapters on Gynecology, Surgery, Laboratory Procedures, Ophthalmology, Dermatology, Psychiatry, Orthopedic Surgery and Ear, Nose and Throat conditions.

The contributors have written in an interesting style and the impression is not of a mere summary of outstanding articles but of thought and integration so that the reader is privileged to have the benefit of the evalu-

ation and interpretation given by authorities.

In all but 3 of the 21 chapters there is an adequate and often very extensive bibliography to enable the reader to pursue further any special interest. The index is excellent. The format facilitates reading and study.

If one may venture a criticism it is this: Why, in this age when a physician's memory is burdened with chemical and proprietary names, must he also learn the term "ataraxics" (not to be found in some general or even medical dictionaries) when the simpler term "tranquilizers" will do as well or better?

TEXTBOOK OF ENDOCRINOLOGY. *Edited by Robert H. Williams, M.D., Executive Officer and Professor of Medicine, University of Washington Medical School, Seattle, Washington. $13.00, pp. 776, W. B. Saunders Company, Philadelphia, August 1955, 2nd ed.*

The field of clinical endocrinology has become so broad in scope that the preparation of an authoritative, well-organized textbook on this subject is a staggering task. The authors of this volume, under the leadership of Robert H. Williams, have succeeded in preparing such a textbook for the student and practicing physicians. The volume illustrates the advantages of multiple authorship, as well as some of the disadvantages.

No single author can write on all aspects of endocrinology with requisite authority. The principal advantage of multiple authorship of this textbook lies in the fact that each writer is an authority on his subject. Thus, the editor, Robert H. Williams, writes on "General Principles of the Physiology of the Endocrines," the "Pituitary," the "Thyroid," and "Diagnosis and Treatment of Endocrinopathies: Hormone Preparations." The editor, together with several of the other authors, writes on "Laboratory Diagnostic and Assay Procedures." Peter H. Forsham and George W. Thorn prepared the chapters on the "Adrenals" and the "Pancreas and Diabetes Mellitus"; John Eager Howard and William Wallace Scott on the "Testes"; George Van S. Smith on the "Ovaries"; Edward C. Reifenstein, Jr., on the "Parathyroids"; Lawson Wilkins on the "Influence of Endocrine Glands Upon Growth and Development"; Harry B. Friedgood on "Neuroendocrinology," and William H. Daughaday on "Obesity." The writings of these authors make up a textbook of endocrinology of high quality.

The material on diabetes mellitus by Forsham and Thorn is effectively presented. The clinical material is preceded by a well-prepared, concise section on fundamental endocrine and metabolic information in relation to diabetes. The clinical material is well organized and presented along lines which are accepted by most of the authorities on diabetes in this country. A section on hyperinsulinism, which was omitted from the first edition, is included in this chapter and deals with the subject in a brief but adequate manner.

One of the principal disadvantages of multiple authorship is the lack of uniformity in style of writing, length of presentation and critical faculty exhibited by the various contributors. For example, the material by the editor himself is written in a thoughtful manner with due consideration to the opinions of others on controversial subjects. Likewise, the chapter on the testes by Howard and Scott is thoughtful and critical in its tone and recognizes the limitations of existing knowledge. (It should be pointed out that this chapter is not as up-to-date as it might be, only 7 of the 82 references being dated later than 1950). By contrast, the chapter on the adrenals by Forsham and Thorn shows a tendency to present more material as established fact than is really known to be fact. Some will regard this as good pedagogy, even though the positive tone is achieved at the expense of complete accuracy. To some extent the dilemma involved in trying to be concise, positive and simple for purposes of good teaching and, at the same time, reasonably accurate is inescapable, but on some points these authors go too far in sacrificing accuracy for simplicity and positivity.

The chapter on the parathyroid glands by Reifenstein is excellent. Perhaps it is disproportionately thorough and lengthy in relation to the other material in the book and to the frequency of diseases of the parathyroid glands. The material by Friedgood on neuroendocrinology is somewhat out of harmony with the rest of the volume in that it deals, in a verbose manner, too much with fantasy and too little with fact. A critical appraisal of what is actually known of neuroendocrine relationships would provide a useful chapter in this volume but the present chapter does not fulfill the requirements.

The chapter by the editor and others on laboratory diagnosis and assay procedures will be of considerable interest to students and practicing physicians who are seriously interested in endocrinology. The final chapter by the editor outlines in a sound manner certain fundamentals in the diagnosis and treatment of endocrinopathies and the use of available hormone preparations.

On the whole, and in spite of the inconsistencies which inevitably accompany multiple authorship, this is an excellent textbook of endocrinology which can be recommended to students and practicing physicians alike.

ABSTRACTS

Albanese, Anthony A.; Orto, Louise; Rossy, Joan; DiLallo, Rosemarie; and Belmont, Aurora (Nutritional Res. Lab., St. Luke's Hosp., New York, N. Y.): EFFECT OF CARBOHYDRATES ON BLOOD AMINO NITROGEN. Metabolism 4:160-65, March 1955.

Not only is fructose much more rapidly metabolized than dextrose, but these studies suggest that fructose is also a readier source than dextrose of carbon structures (hydroxy and ketoacids). These, in turn, are converted to amino acids on combination with labile amino groups. It is suggested that fructose has a greater protein-sparing effect than dextrose.

Beaton, John R. (Dept. of Pub. Health & Nutrition, Univ. of Toronto, Toronto, Canada): FURTHER STUDIES ON CARBOHYDRATE METABOLISM IN THE VITAMIN-B_6-DEPRIVED RAT. Canad. J. Biochem. & Physiol. 33:161-66, March 1955.

After one and three weeks of vitamin B_6 restriction, young Wistar rats of both sexes have significantly higher levels of inorganic phosphorus and glutathione in blood and liver than pair-fed controls. Muscle-glycogen levels remain unchanged. The blood sugar lowering effect of insulin administration on rats deprived of vitamin B_6 is slightly more pronounced than on controls. Alloxan administration elevated the blood sugar levels of the deprived rats to a slightly greater extent than the levels of controls.

Bernard, Jack A. (El Paso, Texas): INSULINS. Southwestern Med. 36:590, December 1955.

The author discusses uses of current insulins, particularly NPH and Lente insulins.

Berry, Robert E. L.; and Flotte, C. Thomas (Dept. of Surg., Univ. of Michigan, Ann Arbor, Mich.): PERIPHERAL ARTERIOSCLEROTIC VASCULAR DISEASE IN DIABETICS. A.M.A. Arch. Surg. 71:460-67, September 1955.

The results from lumbar sympathectomy in ninety-three patients with symptomatic peripheral vascular disease are presented and compared with results in 182 nondiabetic patients. In the absence of ulceration or gangrene, results in nondiabetics are somewhat better than in diabetic patients. After necrosis has developed, the results are essentially the same. Below fifty-five years of age, 48 per cent of diabetics obtained a good result. Above sixty-five, only 12 per cent were benefited. The results in diabetics over sixty-five years of age with significant elevation of blood pressure or central-nervous-system or cardiac involvement were so poor that they represent a contraindication to sympathectomy. Severity, duration, or adequacy of treatment of diabetes little affects the percentage of good results obtained. The amputation rate is higher in inadequately treated and in short-term diabetics. The nature of the vascular lesions and blood lipid changes and the relationship to the higher observed incidence of gangrene in diabetics are discussed.

Bossak, Elaine T.; and Joelson, Robert H. (Dept. of Med., Mt. Sinai Hosp., New York, N. Y.): ACUTE PANCREATITIS COMPLICATING DIABETES MELLITUS. A.M.A. Arch. Int. Med. 97:201-07, February 1956.

Eight instances of acute pancreatitis in patients with known diabetes mellitus were encountered among 106 patients with acute pancreatitis who were hospitalized between 1936 and 1954. The average duration of antecedent diabetes was 7.3 years, the average age was 43 years, and all patients were female. An excessively high mortality was noted in diabetics as compared with nondiabetics. A possible vascular etiology is proposed for the occurrence of acute pancreatitis in patients with known diabetes mellitus. Acute pancreatitis should especially be considered in diabetics with coma resistant to therapy, with abdominal pain or tenderness, or with shock or oliguria.

Bowers, Ralph F. (Surg. Serv., V. A. Med. Teaching Group Hosp., Memphis, Tenn.): DISEASES OF THE PANCREAS; SURGICAL ASPECTS. A.M.A. Arch. Surg. 72:210-17, February 1956.

The author reviews the surgical aspects of diseases of the pancreas under the headings of congenital disorders, injuries, infectious conditions and neoplasms of the pancreas. Recent advances in both experimental and clinical aspects are discussed.

Chase, Lillian A.: THE CHARLES H. BEST INSTITUTE. Canad. M.A.J. 72:468, March 15, 1955.

A brief description of the Charles H. Best Institute, its physical plant, personnel and activities of the various workers is presented.

Eisen, Herman N.; and Tabachnick, Milton (Inst. of Industrial Med., New York Univ., Post-Grad. Med. Sch., New York, N. Y.): PROTEIN METABOLISM. M. Clin. North America 863-79, May 1955.

This is another review article regarding protein metabolism that hits probably the most important highlights in clinical medicine. One table in the article, sum-

marizing the changes in albumin as well as alpha, beta and gamma globulins in various diseases serves as a general review guide in some clinical syndromes. The section regarding protein metabolism in relation to clinical states, such as diabetes mellitus, is too brief for adequate detail.

Elder, T. David; and Baker, Roger Denio (Dept. Path., Duke Univ. Sch. of Med., and the V. A. Hosp., Durham, N. C.): PULMONARY MUCORMYCOSIS IN RABBITS WITH ALLOXAN DIABETES: INCREASED INVASIVENESS OF FUNGUS DURING ACUTE TOXIC PHASE OF DIABETES. A.M.A. Arch. Path. *61*:159-68, February 1956.

The hyphal proliferation in bronchopulmonary lesions of the acute toxic phase of alloxan diabetes in rabbits closely resembles the fulminating pulmonary lesions of human mucormycosis (presumably due to *Rhizopus*) that develop in unregulated and ketotic patients with diabetes mellitus. A difference between the acute toxic and the chronic alloxan diabetes of rabbits is the occurrence of ketosis and lipemia in the former and their absence in the latter. The increased susceptibility to *Rhizopus* infection in the acute phase of alloxan diabetes does not appear to be due to hyperglycemia, failure of inflammatory response to infection or lowered body temperature. Loss of phagocytic ability of macrophages in giant cells, ketosis, devitalization of tissues and changes in white-blood-cell metabolism are suggested as possible causes.

Fabrykant, Maximilian (Dept. of Med., New York Univ. Post-Grad. Med. Sch., and the Fourth Med. Div., Bellevue Hosp., New York, N. Y.): CLINICAL VERSUS LABORATORY HYPOGLYCEMIA: AN ANALYSIS OF 81 ORAL GLUCOSE TOLERANCE TESTS WITH ARTERIAL AND VENOUS BLOOD GLUCOSE MEASUREMENTS. Metabolism *4*:153-59, March 1955.

Oral glucose tolerance tests were carried out in seventy-six patients, thirteen of whom had spontaneous hypoglycemia. The rest had other various conditions associated with hypoglycemia. Weakness and hunger were the commonest of the various symptoms recorded during hypoglycemia in the course of the glucose tolerance tests. Hypoglycemic symptoms occurring during the tests often failed to duplicate those complained of by the patients. The symptoms during the glucose loading test in ten preceded the fall in the blood glucose to its lowest level. Occasionally, subnormal blood-glucose values failed to produce hypoglycemic manifestations. No relationship could be established between the clinical symptoms and the arteriovenous glucose difference.

Ferner, H.; and Runge, W. (Dept. of Anat., Univ. of Hamburg, Germany): SYNTHALIN A AS SELECTIVE MITOTIC POISON ACTING ON ALPHA CELLS OF THE ISLETS OF LANGERHANS. Science *122*:420, Sept. 2, 1955.

The authors report upon the effect of Synthalin A on the alpha cells of young animals as distinguished from its demonstrated partial or total destruction of alpha cells without injury to the beta cells or exocrine pancreas in the adult rat, guinea pig and rabbit. It was observed in one to five-day-old rats that a single subcutaneous injection of synthalin A produced no injury in the one-day-old animals but a significant decrease in mitotic frequency and evidence of mitotic-cell injury from the second to the fifth day. In consequence, the curve of mitotic frequency of the treated animals remained flat as compared with the rising curve of control animals, so that on the fifth day of life, the frequency of dividing alpha cells in the former was only 25 per cent of normal. No mitotic divisions of beta cells or acinar cells were effected.

Fisher, June; Gius, John Armes; and Janes, Ralph G. (Dept. of Int. Med., Surg. and Anat., State Univ. of Iowa, Coll. of Med. and Univ. Hosps., Iowa City, Ia.): ISLET-CELL TUMOR OF THE PANCREAS WITH HYPERINSULINISM. FAILURE OF SURGICAL AND ALLOXAN TREATMENT. REPORT OF A CASE. A.M.A. Arch. Path. *60*:628-34, December 1955.

The authors report a case of hyperinsulinism due to a benign functioning islet-cell tumor. Neither medical nor surgical treatment halted the progress of the disease. Alloxan produced only a temporary elevation of blood sugar and symptomatic relief. The local side reactions of alloxan included pain, swelling, redness, and sclerosis of the veins with occasional venous thrombosis at the site of injection. When large doses of alloxan were given, generalized reactions such as flushing, nausea, and wheezing respirations occurred. Death occurred four days after an alloxan injection of 150 mg./kg. of body weight. The injection was followed by shock, dyspnea, cyanosis, high temperature, jaundice, coma, and death. Autopsy revealed a small islet-cell tumor deep within the remaining pancreatic tissue. There was no histologic evidence of necrosis of islet cells in the tumor or in adjacent normal pancreas that could be attributed to alloxan. The authors feel that there is no reason to believe that alloxan in large doses may have toxic effects on organs other than the pancreas.

Gall, John C.; and Burke, Edmund C. (Sect. on Pediats., Mayo Foundation, Rochester, Minn.): IDIOPATHIC HYPOGLYCEMOSIS: REPORT OF TWO CASES. Proc. Staff Meet. Mayo Clin. *30*:477-83, Oct. 19, 1955.

Two cases are presented of infants having recurrent episodes of marked hypoglycemia associated with con-

vulsions. With inadequate therapy, severe brain damage ensues. Corticotropin has been a successful agent in controlling hypoglycemia.

Gallagher, C. H.; Judah, J. D.; and Rees, K. R. (Dept. of Morbid Anat., University College Hosp., Med. Sch.; Dept. of Biochem., University College, London, England): GLUCOSE OXIDATION BY BRAIN MITOCHONDRIA. Biochem. J. 62:436-40, March 1956.

A study of rat-brain mitochondria has shown that these structures possess properties not found in the mitochondria of liver, kidney and heart, in that the former are capable of oxidizing glucose completely to carbon dioxide and water. Calcium inhibits the oxidation of citrate by freshly prepared liver and kidney mitochondrial preparations, whereas it stimulates citrate oxidation by brain mitochondrial preparations.

Geiger, E.; and Pinsky, J. J. (Depts. of Pharmacol. and Physiol. of the Univ. of Southern California Med. Sch., Los Angeles, and Van Camp Labs., Terminal Island, Calif.): UTILIZATION AND NITROGEN-SPARING EFFECT OF FRUCTOSE IN ALLOXAN DIABETIC RATS. Metabolism 4:166-73, March 1955.

The alloxan-diabetic rat shows greater utilization of fructose than of glucose. The protein-sparing effect of fructose in alloxan-diabetic rats is considerable, whereas the effect of glucose is much less.

Goldner, Martin G. (Depts. of Med. of the State Univ. of New York Coll. of Med. at New York City and the Jewish Chronic Disease Hosp., Brooklyn, N. Y.): FAT METABOLISM, OBESITY AND HYPERCHOLESTEROLEMIA. M. Clin. North America 845-62, May 1955.

This is a review summarizing, in a very compact form, some of the biochemical factors influencing fat metabolism and relating these in very realistic fashion to some of the clinical problems of obesity, arthrosclerosis, et cetera. The discussion of athrogenesis, hypercholesterolemia and hyperlipemia is somewhat too brief for adequate evaluation but, nevertheless, the article serves to consolidate the more concrete evidence compiled to date.

Gould, Kenneth S.; and Shlevin, Edmund L. (Jewish Hosp., Brooklyn, N. Y.): ADDISON'S DISEASE COMPLICATING DIABETES MELLITUS IN ADOLESCENCE. Ann. Int. Med. 43:1092-99, November 1955.

The authors present a case of diabetes mellitus in an adolescent, complicated by Addison's disease. Autopsy findings are described, and etiologic factors are discussed. Characteristic blood electrolyte disturbances, their response to therapy, and changing insulin requirements in a diabetic who becomes an Addisonian are demonstrated.

Gumpel, Roy C.; and Lipton, Philip (Med. Service, V. A. Hosp., Newington, Conn.): XANTHOMA DIABETICORUM. A.M.A. Arch. Int. Med. 96:560-64, October 1955.

A case of xanthoma diabeticorum is reported that includes the findings of biopsies of the skin and liver. Ordinary measures of diabetic control, with no reduction of dietary fat, resulted in a striking response of the skin lesions and of fatty liver. Xanthoma diabeticorum dramatically calls attention to the disturbed fat metabolism of uncontrolled diabetes, which presumably plays a part in the high incidence of vascular disease accompanying diabetes mellitus.

Hellman, Bo; and Diderholm, Hans (Histological Dept., Univ. of Upsala, Sweden): THE DIABETOGENIC EFFECT OF ALLOXAN AFTER ELIMINATION OF EXTRA-PANCREATIC FACTORS. Acta endocrinol. 20:81-87, September 1955.

The authors have attempted to eliminate extrapancreatic factors in evaluating the diabetogenic effect of alloxan. In the present investigation, alloxan was injected into the pancreatic artery just inside the clamped portion, which was kept isolated for five minutes. Extrapancreatic factors were prevented in the following three ways: (1) Such factors could not reach the clamped portion during the critical period; (2) the small doses required gave a high local concentration of alloxan in the pancreas, preventing effects in other parts of the organism; and (3) the retained drug was converted into inactive compounds before leaving the temporarily clamped portion. By this procedure it was found possible to produce necrosis of the beta cells in the absence of extrapancreatic influences by only a moderate amount of alloxan in comparison with that required when it is injected systemically. The exocrine portion of the pancreas was not affected. The distribution of islets with necrotic beta cells supports the view that alloxan has a direct effect upon the beta cells. It was found that 6.4 mg. per kg. of alloxan was sufficient to produce degenerative effects in the beta cells.

Henderson, Margaret J.; Wrenshall, Gerald A.; and Odense, Paul (Banting and Best Dept. of Med. Res. and the Dept. of Biochemistry, Univ. of Toronto, Toronto, Canada): EFFECTS OF INSULIN ON RATES OF GLUCOSE TRANSFER IN THE DEPANCREATIZED DOG. Canad. J. Biochem. & Physiol. 33:926-39, November 1955.

By use of a new experimental approach, an attempt has been made to answer the question as to whether insulin acts to lower blood glucose by increasing utilization or by decreasing production or both. A trace dose of radioactive glucose was injected into each of six

postabsorptive depancreatized dogs that had been deprived of exogenous insulin for sixty-six hours. Blood samples were collected before and after the intravenous injection of insulin, and plasma glucose concentration and specific activity were measured. From these data, the simultaneous rates of appearance and disappearance of plasma glucose were calculated in absolute units for a sequence of time intervals, both before and after insulin, by a method that did not assume dynamic equilibrium. The method described in this paper had made it possible to follow the effects of insulin while it was acting in the same animal. Insulin was found to cause an abrupt and marked increase in the rate of disappearance of glucose, and this increased rate became less with time, reaching the preinsulin level in about ninety minutes. Insulin caused a slower and much smaller decrease in the rate of appearance, but the decrease became greater with time during the three-hour period of observation. Thus, it appeared that insulin acted in vivo both to increase the utilization of glucose and to decrease its production, but the effects differed in magnitude and in speed of response.

Herrmann, E. (Dept. of Med., Inselspital Berne, Switzerland): DIABETES INSIPIDUS MASKED THROUGH FAILURE OF THE ANTERIOR PITUITARY LOBE. Schweiz. med. Wchnschr. *85*:1041-45, Oct. 22, 1955.

The full clinical picture of diabetes insipidus demands the presence of a normal functioning anterior pituitary lobe. Two boys and one man with typical diabetes insipidus are described. The gradual development of anterior pituitary insufficiency made the diabetes insipidus disappear in one case completely, in two cases almost completely. When ACTH or cortisone was applied to the two boys, diabetes insipidus reappeared. (German)

Jones, Walter S. (Providence Lying-In Hosp., Providence, R. I.): THE SEVERITY OF DIABETES IN PREGNANCY. Am. J. Obst. & Gynec. *71*:318-25, February 1956.

A study of 204 viable pregnancies with diabetes was made in an attempt to arrive at a severity index; it indicated that insulin requirement is of less importance than the criteria laid down by the White Pregnancy Risk Classification.

Keeney, Arthur H.; and Mody, Mansukhlal V. (University of Louisville School of Medicine, Louisville, Ky.): ADRENOSEM (CARBAZOCHROME) IN PRIMARY GLAUCOMA AND DIABETIC RETINOPATHY. A.M.A. Arch. Ophth. *54*:665-69, November 1955.

Eleven patients with primary glaucoma, thirteen with diabetic retinopathy and fourteen control patients have been studied for correlation of capillary function with their ocular disease. Alternate members of these groups have also been treated with carbazochrome (Adrenosem) or identical-appearing placebo tablets. The diabetic retinopathy patients all had Grade 1 to 3 fundus changes, and none showed alterations on carbazochrome or placebo medication. Average lymph flow values (8 mm.) were slightly lower than in the control group (11 mm.) but generally remained stable and reflected no changes with medication. Capillary loop counts were essentially the same as in the control group, and they were also uninfluenced by the drugs used. Under the conditions of this study, carbazochrome could not be demonstrated to have significant effect on intraocular tension, the coefficient of facility of aqueous outflow, diabetic retinopathy, cutaneous lymph flow, capillary counts or capillary mobilization.

Kinash, B.; and Haist, R. E. (Dept. of Physiol., Univ. of Toronto, Toronto, Canada): THE INFLUENCE OF THE THYROID GLAND ON THE ISLETS OF LANGERHANS AND THE PANCREAS. Canad. J. Biochem. & Physiol. *33*:380-84, May 1955.

When diet containing 0.25 per cent desiccated thyroid gland was fed ad libitum to intact or hypophysectomized rats, there was a statistically significant increase over pair-fed controls in the weight of the pancreas, weight of the islets of Langerhans and islet weight per unit of body weight. In intact rats the concentration of islet tissue in the pancreas was not significantly altered, but in hypophysectomized animals the concentration of islet tissue in the pancreas was reduced because of the large increase in pancreas weight. The great reduction in pancreas weight occasioned by hypophysectomy was prevented to a large extent by the administration of desiccated thyroid gland. This would seem to indicate that a large part of this effect of hypophysectomy on the external-secreting portion of the pancreas is associated with altered thyroid function, although it is unlikely that this is the sole factor involved.

Kinsell, Laurance W.; Brown, Frederick R., Jr.; Friskey, Roger W.; and Michaels, George D. (Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.): INSULIN-SPARING SULFONAMIDES. Science *123*: 585, April 6, 1956.

The authors report upon six "severe" and four "mild" diabetics treated with one or both of the blood sugar lowering sulfonamides: BZ-55 (N_1-sulfanilyl-N_2-n-butyl-carbamide), in doses ranging from 1 to 16 gm. daily, and Orinase (a compound identical with BZ-55 except for the substitution of a methyl for the amino

group on the benzene ring), in doses ranging from 1 to 6 gm. per day. Three of the five "severe" diabetics had very significant decrease in insulin requirement and lowering of blood or urine sugar on a constant dose of insulin. Two grams or more of sulfonamide per day were required to produce this effect. In these diabetics, a reciprocal relationship was noted between blood-free sulfonamide and blood sugar. One "severe" diabetic had a significant increase in glycosuria during sulfonamide administration, and one "severe" diabetic had essentially no demonstrable effect. All sulfonamide administered could be accounted for in the urine of two "severe" juvenile diabetics, one of whom had a profoundly favorable modification of the diabetes and the other a significant increase in glycosuria. In the former, the greater portion of urinary sulfonamide was conjugated; in the latter, the greater portion was free, suggesting that differential metabolisms of the administered sulfonamide may determine the type of therapeutic response. Three middle-aged obese diabetics had more than a 50 per cent reduction in insulin requirement on sulfonamide administration of less than 2 gm. daily. One "mild" diabetic maintained without insulin had a 50 per cent reduction in blood sugar level on a day on which she received 3 gm. of sulfonamide. Six grams of sulfonamide reverted a diabetic glucose-tolerance test to normal in one "preclinical" diabetic. Intensive sulfonamide administration in three "severe" diabetics resulted in a reduction of twenty-four-hour I^{131} uptake by the thyroid to less than 5 per cent, with return of the uptake to a normal level upon reduction in dosage. Very large dosages of sulfonamides were associated with decrease in arcualating granulocytes, and marrow findings were interpreted as showing marrow arrest. The blood count returned to normal when medication was decreased or stopped.

Kritzer, Morton D.; Shrifter, Norman; and Demetriou, James A. (Depts. Med. and Pharmacol., Univ. of Southern California Sch. of Med., and Diabetic Clin., Los Angeles Co. Gen'l. Hosp., Los Angeles, Calif.): CARBOHYDRATE METABOLISM: I. A STUDY OF CHANGES IN SERUM INORGANIC PHOSPHORUS DURING GLUCOSE-TOLERANCE TEST IN NORMALS, DIABETICS AND PREDIABETIC WOMEN. A.M.A. Arch. Int. Med. 97:62-67, January 1956.

After the intravenous administration of glucose, a greater and earlier drop in phosphate is noted in the normal as compared with the diabetic. The procedure is statistically valid for groups but inapplicable for individual patients. This difference in the phosphate levels in normals and diabetics is not present when the glucose is administered by the oral route. Following oral glucose, the marked drop noted in the normal phosphorus curve with the intravenous route is absent. It is postulated that, after oral glucose, the interposition of the liver abolishes the phenomenon noted in the normal when the intravenous route is employed. This indirectly implicates the peripheral tissues as the site of phosphate utilization.

Lawrence, R. D. (London, England): THREE TYPES OF HUMAN DIABETES. Ann. Int. Med. 43:1199-1208, December 1955.

The author describes three types of human diabetes, all of which show hyperglycemia and glycosuria. The differentiating factors include an excess or lack of stored body fat, the presence or absence of ketosis, and the presence of varying amounts of blood insulin during life or extractable insulin from the pancreas after death. The three types of diabetes are described as (1) lipoplethoric, (2) insulin-deficient, and (3) lipo-atrophic. The fundamental differences of these types of diabetes mellitus are discussed.

Luft, R.; Olivecrona, H.; von Euler, U.; Ikkos, D.; Ljunggren, H.; Nilsson, L. B.; Sekkenes, J.; Sjögren, B.; and Waschewsky, H. J. (Serafiner Hosp., Stockholm, Sweden): ENDOCRINE INSUFFICIENCIES AFTER HYPOPHYSECTOMY IN MAN. Helvet. med. acta. 22:338-50, November 1955.

Total hypophysectomy is followed by transitory diabetes insipidus and permanent thyroid and adrenocortical insufficiency, but the function of the adrenal medulla is not affected by the operation. (German)

Lukens, F. D. W. (George S. Cox Med. Res. Inst., Univ. of Pennsylvania, Philadelphia, Pa.): THE USE OF LABORATORY TESTS IN DIABETES. J. Clin. Endocrinol. 16:272-79, February 1956.

The author reviews the pertinent laboratory tests that are of help in the management of diabetic patients, with the indications and limitations for each of these.

McLaughlin, B. G.; and Bradley, R. F. (Manchester, N. H., and Boston, Mass.): SUDDEN MAJOR ARTERIAL OCCLUSION IN THE UPPER EXTREMITY OF A DIABETIC: CASE REPORT. Ann. Int. Med. 43:1330-34, December 1955.

The authors report an instance of sudden major vessel occlusion in the arm of a diabetic patient. Similar cases are reviewed in both nondiabetic and diabetic populations in thirty-one years of hospital admissions. Sudden occlusion of a major vessel in the upper extremity is quite rare. Whenever it occurs without evident cause, diabetes should be suspected. Widespread vascular disease may appear at a comparatively early age in cases of supposedly mild diabetes.

Miller, Max; and Craig, James W. (Dept. of Med., Sch. of Med., Western Reserve Univ., and Lakeside Hosp., Cleveland, O.): HYPOGLYCEMIC EFFECTS OF 1-BUTYL-3-P-TOLUENE SULFONYLUREA GIVEN ORALLY IN HUMAN DIABETIC SUBJECTS (A PRELIMINARY REPORT). Metabolism 5:162-64, March 1956.

This drug was reported to be of success in a middle-aged obese female and to show some success in an eighteen-year-old girl, in that the insulin requirement dropped from 2,000 to 500 units of insulin per day with improvement in control. A case of subtotal pancreatomy diabetes also was aided by this therapy.

Miller, William L., Jr.; and Dulin, William E. (Depts. of Pharmacol. and Endocrinology, Upjohn Company, Kalamazoo, Mich.): ORINASE, A NEW ORAL HYPOGLYCEMIC COMPOUND. Science *123*:584-85, April 6, 1956.

The authors report upon the effect of 1-butyl-3-p-tolylsulfonylurea (Orinase) on the blood sugar and on liver and muscle glycogen of fasted rats, dogs and rabbits. In comparison to fasting blood sugar levels, a single oral dose of 270 mg./kg. of Orinase administered to twenty-four-hour-fasted male rats produced a substantial decrease in blood sugar in one-half hour, a maximum fall of 25 to 30 per cent in two hours, and a maintenance of the decreased blood sugar level for at least six hours. At seven hours, the liver glycogen was increased in the Orinase animals, whereas the muscle glycogen was not changed from the control value. In contrast, insulin in doses of 6.7 and 13.4 units/kg. produced a substantial increase in muscle glycogen with no consistent change in liver glycogen. Synthalin, a liver poison with hypoglycemic effects, depresses the liver glycogen. In fasted dogs, a single dose of 25 mg./kg. decreased the blood sugar and maintained it at a level 25 to 30 per cent below controls for twenty-four to thirty-two hours, and a dose of 100 mg./kg. resulted in a decrease of 40 per cent for twenty-four to thirty-two hours. Plasma level determinations of Orinase in dogs indicated that, at the peak, about 10 per cent of the dose is in the plasma and that twenty-four to seventy-two hours are required to clear the plasma. Rabbits given 400 mg./kg. responded with maximum blood sugar depressions similar to those obtained with 100 mg./kg. in dogs. Chronic toxicity studies in rats revealed no change in hemograms at four weeks, but a moderate enlargement of the thyroid gland was observed in all rats given the higher doses.

Mirsky, I. Arthur; Diengott, Daniel; Dolger, Henry (Dept. of Clin. Sc., Sch. of Med., Univ. of Pittsburgh, Pittsburgh, Pa.): HYPOGLYCEMIC ACTION OF SULFONYLUREAS IN PATIENTS WITH DIABETES MELLITUS. Science *123*:583-84, April 6, 1956.

The authors report that a hypoglycemic reponse of statistically high significance occurred in thirty-four of forty-four adult diabetic patients given 50 mg. of tolylsulfonylurea (Orinase) by mouth per kilogram of body weight. The blood sugar values were determined at hourly intervals up to five hours; maximum reductions up to 45 to 60 per cent of the pretest values occurred at the fourth and fifth hours. The patients studied varied from twenty-one to seventy-three years in age, with the duration of the metabolic disorder ranging from less than one year to thirty years and the age at onset between six and sixty-five years. The ten subjects who did not respond significantly to the ingestion of the tolylsulfonylurea developed the metabolic disorder before the age of twenty years. Although the response appears to bear a direct relationship to the age at which the diabetic syndrome developed, the duration of the diabetes also plays a role in determining the response. The data support the hypothesis that the insulin insufficiency of approximately 75 per cent of patients with diabetes mellitus is due to an increase in the rate of destruction of insulin by the tissues and that the tolylsulfonylurea drug acts as an inhibitor of endogenous insulin destruction, with a consequent increase in the availability of insulin and a resultant hypoglycemia.

Mirsky, I. Arthur; and Perisutti, Gladys (Dept. of Clin. Sc., Sch. of Med., Univ. of Pittsburgh, Pittsburgh, Pa.): EFFECT OF INSULINASE: INHIBITOR ON HYPOGLYCEMIC ACTION OF INSULIN. Science *122*:559-60, Sept. 23, 1955.

The authors report that an insulinase-inhibitor prepared as a nonprotein fraction from beef liver, which inhibits the destruction in vitro and in vivo of I^{131}-labeled insulin, is effective also in enhancing the hypoglycemic action of insulin in rats and in rabbits upon subcutaneous administration in a dose of 2 gm./kg. The insulinase-inhibitor preparation was nontoxic for rats in a dosage of 10 gm./kg. but usually fatal to rabbits in a dosage as low as 1 gm./kg. of body weight.

Mirsky, I. Arthur; Perisutti, Gladys; and Diengott, Daniel (Dept. of Clin. Sc., Sch. of Med., Univ. of Pittsburgh, Pittsburgh, Pa.): THE INHIBITION OF INSULINASE BY HYPOGLYCEMIC SULFONAMIDES. Metabolism 5:156-61, March 1956.

Suggestive evidence is presented that two aryl sulfonylureas, U6987 and U2043 (carbutamide and tolbutamide), lead to hypoglycemia in normal rats by a reduction in insulinase activity. This action appears to be a noncompetitive inhibition of insulinase.

Moschcowitz, Eli (Labs., Dept. of Path., The Mount Sinai Hosp., New York, N. Y.): THE PATHOGENESIS OF THE HYALINIZATION OF THE ISLANDS OF LANGERHANS. A.M.A. Arch. Path. *61*:136-42, February 1956.

The author states that the island lesions in adult diabetes mellitus are nearly always associated with arteriosclerosis of the pancreatic vessels and that they may be interpreted as capillary sclerosis, precisely comparable to that found in the alveolar capillaries of the lung, in the sinusoids of the liver and in the glomeruli in the presence of arteriosclerosis or phlebosclerosis affecting the main supplying vessels of these organs. The capillary sclerosis is the result either of the extension of the fibrosing or hyalinizing lesion from the afferent arteriole of the island into the capillaries or of a diminution of the blood supply. Island lesions in adult diabetes occur in a little less than half the cases. They do not occur more frequently because of the special freely anastomosing pattern of both the grosser and the capillary blood supply of the pancreas and of the islands. The cause of the hypoinsulinemia in the cases in which the islands are intact is ascribable to an insufficiency, consequent to an impairment of the grosser blood supply. In juvenile diabetes, in which island lesions are very rare if not entirely absent, the cause of the diabetes cannot be explained anatomically.

Murray, Ian (Dept. Metabolic Diseases, Victoria Infirmary, Glasgow, Scotland): THE NEWER INSULINS. Practitioner *175*:502-07, October 1955.

The original claim made for the Lente insulins was that 90 per cent of diabetics could be controlled with a single daily injection. A more recent report from Denmark showed this to be possible in 990 of 1,030 patients, of whom 70 per cent had previously received two injections a day; Lente insulin sufficed in 80 per cent, whereas additional Ultralente was required by 11 per cent and Semilente by 9 per cent of the patients. In general, various other workers have substantiated these claims. Experience with these insulins has demonstrated that they possess certain advantages. There is no doubt that they are much less liable to produce the local allergic reactions that are not infrequent with the use of protamine zinc insulin. This allergy is occasionally encountered with the Lente insulins but is nearly always of less degree and is transient. This is a matter of considerable importance and it would make the new preparations preferable to protamine zinc insulin even if all else were equal. But a high proportion of patients, who would probably require a mixture of soluble and protamine zinc insulins, can be controlled on Lente insulin and thus avoid the more complicated injection technic involved with the former. This is particularly true of new patients, in probably 90 per cent of whom Lente gives satisfactory control. Changing a patient to the new insulins for one of the reasons already discussed presents some difficulties and is not devoid of risk unless these are recognized. First, it is necessary to have the full cooperation of the patient as regards diet and performance of frequent urine tests. It is important to recognize that in many cases the dose of Lente insulin must be considerably greater than the dose of the insulin previously taken. When a patient is transferred to Lente on his former dosage, it is often found that for the next few days glycosuria becomes much worse, and he may develop diabetic symptoms. Some patients become so disturbed by this development that they resume their former regimen before the dose can be increased. Such patients account for some of the failures with Lente insulin, although doubtless some of these might have been controlled had the dosage been adequately raised. This increased requirement is encountered most often when the patient has previously been taking protamine zinc alone, but it is found also when the former insulin has been a mixture of soluble and protamine zinc insulins or even when two doses of soluble insulin have been taken. The amount of this increase in dosage may be large: 50 to 100 per cent or even more. The reason for this increased insulin requirement when change is made to Lente is not clear. Undoubtedly, in the case of patients formerly taking protamine zinc insulin, it is partially explained by the fact that the dose of the latter could not be increased because of liability to nocturnal attacks of hypoglycemia, although diurnal control was relatively poor compared with that effected by insulin-zinc suspension. It was originally suggested that hypoglycemic reactions were less severe with the use of the Lente insulins than with the older insulins. Further experience has shown that this is not true. Some diabetics are too unstable or too "brittle" to be controlled on a single daily dose of insulin, and they consequently require two injections a day, a regimen that gives considerably more flexibility of control. Because these unstable diabetics are often extremely difficult to control, various permutations and combinations may be tried in an endeavor to discover the treatment most suitable for the individual. Some of these patients do quite well on Semilente night and morning. Occasionally two injections a day of Lente may be found to give satisfactory results. It may appear from what has been said that there are many disadvantages in the use of these insulins, but it is not intended to convey this impression. Most workers who have had considerable experience with the Lente insulins

are, in fact, agreed that they represent an advance in insulin treatment. It is generally accepted that the introduction of more insulins leads to confusion, and it has been truly said that "before new insulins are introduced it should be clearly apparent that they possess decisive advantages over those now available." It can be asserted that Lente has definite advantages over protamine zinc insulin. Accordingly, it is to be hoped that eventually protamine zinc will be supplanted. Such a change, however, must be gradual, since patients already well controlled with it, either alone or mixed with soluble insulin, will continue to use protamine zinc. Since Lente is a useful and desirable addition, it follows that Semilente and Ultralente are needed for patients who require proportions other than the 3:7 of Lente. Semilente has an action comparable to that of globin, and one feels that the latter could be abandoned easily. Soluble insulin, however, remains essential, particularly in the treatment of ketosis.

Newcomb, Alvah L. (Winnetka, Ill.): THE NEWBORN OF DIABETIC MOTHERS. Am. J. Obst. & Gynec. 71: 74-77, January 1956.

The factors contributing to fetal loss are discussed, and suggestions for the care of the newborn infant are presented.

Paul, Jerome T. (Chicago, Ill.): THE SIGNIFICANCE OF RENAL GLYCOSURIA IN PREGNANCY. Am. J. Obst. & Gynec. 71:70-73, January 1956.

Renal glycosuria must be differentiated from diabetes mellitus and, in the last six weeks of pregnancy, from lactosuria. It is suggested that renal glycosuria during pregnancy is not a "benign" condition, since Miller et al., in 1944, reported four fetal deaths among eleven cases showing glycosuria.

Pincus, I. J.; and Snedecor, James G. (Dept. of Physiol. and Div. of Endocrine and Cancer Res., Jefferson Med. Coll. and Dept. of Gastroenterol., Grad. Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.; Dept. of Zool., Univ. of Massachusetts, Amherst, Mass.): GLUCAGON. Metabolism 5:150-55, March 1956.

The paper is a general review of our present knowledge of glucagon.

Pines, Kermit L. (Dept. of Med., Coll. of Physicians & Surgeons, Columbia Univ., Presbyterian Hosp., New York, N. Y.): CARBOHYDRATE METABOLISM. M. Clin. North America 831-44, May 1955.

This very excellent review article summarizes the highlights of carbohydrate metabolism in terms of clinical diabetes mellitus, stressing particularly the biochemical reactions of glycolysis and of the tricarboxylic acid cycle. Dr. Pines also includes a brief but accurate description of endocrine and other factors playing a role in carbohydrate metabolic regulation, and he discusses some of the investigative work regarding the possible location of fundamental defects in diabetes mellitus. The manner in which he relates the alternate pathways of carbohydrate metabolism to the well-known cycles of metabolism and to other factors influencing carbohydrates is excellent. This article is not as detailed as would be desired by the physician entirely conversant with diabetes and its various aspects; but it nevertheless forms a good brief review, particularly of the various factors in the regulation of carbohydrate metabolism.

Robinson, Alan S. (Med. Dept. Jefferson Med. Coll. Hosp., Philadelphia, Pa.; currently resident in Med., Bellevue Hosp., New York, N. Y.): ACUTE PANCREATITIS FOLLOWING TRANSLUMBAR AORTOGRAPHY: CASE REPORT WITH AUTOPSY FINDINGS SEVEN WEEKS FOLLOWING AORTOGRAM. A.M.A. Arch. Surg. 72:290-94, February 1956.

The authors report a case of acute necrotizing pancreatitis following translumbar aortography. This untoward response was probably due to an excessive concentration of dye in the celiac axis. Injection of a small amount of sodium aceprizoate (sodium aceprizoate: category, radiopaque medium; dose, injection intravenous 25 ml. of a 30 per cent solution) to check the position of the needle would probably have avoided the complication, and it is recommended that this be done in all aortographic procedures.

Schirmer, Jacob F.; Caris, Timothy N.; Bowers, Warner F.; and Blount, Robert E. (Brooke Army Hosp., Fort Sam Houston, Texas): CUSHING'S SYNDROME TREATED BY BILATERAL TOTAL ADRENALECTOMY. U. S. Armed Forces M. J. 7:272-77, February 1956.

This is a case report of a twenty-nine-year-old male showing all the clinical manifestations of Cushing's syndrome other than osteoporosis. The investigative studies suggested, as the etiological factor, bilateral adrenal cortical hyperplasia, although the excretory urogram with retroperitoneal air insufflation revealed some displacement downward of the left kidney by a mass in the adrenal area. Following total bilateral adrenalectomy, the various manifestations of the Cushingoid state disappeared, and the patient has been satisfactorily maintained on 25 mg. of cortisone daily.

Stapleton, Thomas (Paediat. Unit, St. Mary's Hosp. Med. Sch., London, England): THE PATTERN OF THE ELECTROLYTE IN THE URINE OF BABIES BORN TO DIABETIC MOTHERS. Arch. Dis. Childhood 31:42-43, February 1956.

The electrolyte excretion in the urine during the first three days of life of five babies born to diabetic mothers was studied. When the excretion in milliequivalents per kilogram of lowest weight during the first three days after birth was used as the standard for comparison, no abnormality in the excretion of sodium, potassium or chloride was found. The differences in electrolyte excretion between cases could all be accounted for by differences in the gestational age.

Tagnon, R. F.; and Devreux, S. (Lab. of Exper. Med. and Dept. of Int. Med., Univ. of Brussels, Brussels, Belgium): EFFECT OF INTRAVENOUS INJECTION OF FRUCTOSE, WITH AND WITHOUT ACTH ADMINISTRATION, ON THE LEVEL OF BLOOD GLUCOSE. J. Clin. Endocrinol. *15*:1475-81, December 1955.

Intravenous injection of fructose did not induce hyperglycemia in normal subjects, but hyperglycemia was regularly induced when ACTH was given prior to fructose. The rate of removal of fructose from the blood was not affected by its previous injection. Fructose was normally removed from the blood in diabetics, regardless of administration of ACTH, and elevation of the blood glucose level resulted with or without ACTH. The authors conclude that the hyperglycemia following administration of ACTH to normal subjects receiving fructose indicates that fructose is converted to glucose in the body. They emphasize the importance of measuring the blood glucose level of patients in a condition of stress who are receiving fructose infusions.

Tonks, D. B.; and Allen, R. H. (Lab. of Hygiene, Dept. of National Health and Welfare, Ottawa, Canada): THE ACCURACY OF GLUCOSE DETERMINATION IN SOME CANADIAN HOSPITAL LABORATORIES. Canad. M.A.J. 72:605-07, April 15, 1955.

Glucose solutions and protein-free blood filtrates accurately analyzed or prepared were sent to various hospital laboratories throughout the province of Ontario. The results obtained from the various laboratories showed rather wide variations.

Van Itallie, Theodore B. (Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.): GLUCAGON: PHYSIOLOGIC AND CLINICAL CONSIDERATIONS. New England J. Med. *254*:794-803, April 26, 1956.

On the basis of existing evidence, it is probable that glucagon is a hormone originating in the alpha cells of the pancreas, and that it is involved in carbohydrate homeostasis. Since patients and laboratory animals deprived of their pancreases can function reasonably well with insulin replacement therapy alone, it is clear that the role of glucagon, whatever it may be, is not indispensable. However, it seems significant that insulin sensitivity and susceptibility to ketosis tend to be greater in such depancreatized patients and animals than in other forms of diabetes. It is generally agreed that glucagon stimulates hepatic glycogenolysis by increasing the concentration of active phosphorylase in liver. As far as is known at present, this is its only primary action. It has been demonstrated in a number of studies that glucagon is not an insulin antagonist in the sense that it interferes with the effect of insulin on the rate of transfer of glucose into cells. Indeed, there is some indication that glucagon administration may actually promote peripheral glucose uptake. Further studies to clarify this point are needed. Other reported metabolic effects of glucagon have not been shown to be independent of its effect on liver glycogenolysis. Since glucagon raises blood glucose by stimulating hepatic glycogenolysis, its clinical usefulness as a means of estimating liver glycogen content, distinguishing between different types of diabetes, testing liver function and diagnosing glycogen-storage disease is being explored. Glucagon also is being used in studies on the physiologic effects of hyperglycemia, with particular reference to the relationship between hyperglycemia and satiety. Very little work involving chronic administration of glucagon has been reported; until studies of this kind become available, appreciable gaps in knowledge of the metabolic effects of glucagon will remain. Progress in this direction has been hampered by lack of a suitable long-acting preparation. Moreover, the development of a reliable method for assaying glucagon in blood would be extremely valuable in providing information about the normal role of glucagon in carbohydrate metabolism. Important advances in the area of glucagon research may be expected when these two technical problems have been solved.

Vaughan, Martha (Sect. of Metabolism, Lab. of Cellular Physiol. and Metabolism, National Heart Inst., National Institutes of Health, Bethesda, Md.): IN VITRO STUDIES ON THE ACTION OF SULFONAMIDE HYPOGLYCEMIC AGENTS. Science *123*:885-86, May 18, 1956.

The author reports no effect of Orinase or BZ-55 on the activity of rat-liver insulinase prepared either as a whole rat-liver homogenate or as a partially purified preparation. Orinase also had no effect on glucose-6-phosphatase activity in homogenates of rat or rabbit liver. Glucose released from rat- and rabbit-liver slices in vitro was studied and the observation made that, in the presence of Orinase, the effect of epinephrine on enhancing release of glucose is markedly diminished. A similar effect was noted upon the action of glucagon in experiments in which amorphous insulin made by Eli Lilly and Company was the source of glucagon activity.

The author suggests that Orinase may exert its hypoglycemic effect with preservation of liver glycogen by inhibiting the enzyme system postulated by Sutherland to be active in phosphorylations of liver glycogen and hepatic output of glucose. This enzyme system is inactivated by a phosphokinase. Epinephrine and glucagon act by stimulating the phosphokinase system; the author hypothesizes that Orinase inhibits phosphokinase so that it cannot be activated by epinephrine or glucagon.

Waife, S. O. (Bureau of Med. and Surg., Dept. of the Navy, Washington, D. C.): PRESENT STATUS OF GLUCAGON. U. S. Armed Forces M.J. 7:313-19, March 1956.

The author offers a short and concise review of the present thoughts on the origin and action of glucagon. He also discusses the eventual role of this compound in the treatment of diabetes mellitus and other conditions revealing disturbances of carbohydrate metabolism.

West, Kelly M. (Oklahoma City, Okla.): THE CHARACTERISTICS AND USES OF LENTE INSULIN. J. Oklahoma M.A. 49:35-37, February 1956.

The chemistry and the characteristics of the activity of Lente insulin are described.

White, Priscilla; Gillespie, Luke; and Sexton, Lloyd (Joslin Clin., Boston, Mass.): USE OF FEMALE SEX HORMONE THERAPY IN PREGNANT DIABETIC PATIENTS. Am. J. Obst. & Gynec. 71:57-69, January 1956.

This paper redefines the indications and results of female sex-hormone therapy in the diabetic pregnancy. It also discusses the White Pregnancy Risk Classification in diabetes and Dr. White's further measures in the management of pregnancy in the diabetic. The value of replacement-hormone therapy is defended not only for its relationship to increased fetal survival but is said to give (1) protection to the progression of diabetic retinopathy and nephropathy, (2) possible protection to the future development of coronary heart disease, and (3) an improved outlook for the future diabetic course of these patients.

Wüthrich, F.; and Reubi, F. (Med. policlinic, Univ. of Berne, Switzerland): RENAL GLYCOSURIA IN MEN AND RABBITS AFTER POISONING WITH POTASSIUM FERRICYANIDE AND OTHER Fe+++ COMPOUNDS. Helvet. med. acta. 22:389-94, November 1955.

The ingestion of 60 to 100 gm. of potassium ferricyanide as a suicidal agent produced in a nineteen-year-old man severe normoglycemic glycosuria with transitory reduction of glomerular filtration, renal blood flow and tubular reabsorption (TmG). Glycosuria at normal blood sugar levels was produced experimentally in rabbits poisoned with potassium ferricyanide. The same effect could be obtained with ferric ammoniumsulfate. (German)

Besides differentiation between fat and muscle in the gross body weight, variations in the water content of the body must be considered. In ascites 5 to 10 kg. of fluid in the abdominal cavity may be encountered and much larger totals of edema fluid are not rare. One of Simonart's[1] starved patients lost 20 kg. in a week while his nutriture was improving and this is by no means unique. Extreme edema is readily detected but more moderate variations in hydration are not clinically recognizable, short of departures from normality of the order of 5 to 10 per cent of the total body weight as water. In severe undernutrition, edema tends to be clinically recognizable only when the relative excess of extracellular fluid, as estimated by the thiocyanate method, approaches 10 per cent of the total body weight.[2] The variable contribution of water to the total body weight of clinically healthy persons is frequently indicated in the weight fluctuations seen on reducing diets under controlled conditions.[3] Under ordinary circumstances an uncertainty of as much as 10 lb. of body weight (in the ordinary adult) may be attributed to hydration variability.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "Body Weight, Body Composition and Calorie Status" by Ancel Keys, Ph.D., p. 15

[1] Simonart: Acta Med. Belg., Bruxelles, Maloine, Paris, 1948, 262 pp.

[2] Keys, Taylor, Mickelsen, and Henschel: Science 103:669, 1946.

[3] Newburgh: A.M.A. Arch. Int. Med. 70:1033, 1942.

ORGANIZATION SECTION

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PAST PRESIDENTS

RANDALL G. SPRAGUE, M.D., *Rochester, Minn.;* HENRY B. MULHOLLAND, M.D., *Charlottesville, Va.;* HENRY T. RICKETTS, M.D., *Chicago*

The Sixteenth Annual Meeting

The Sixteenth Annual Meeting of the American Diabetes Association was held in Chicago, Illinois, June 9-10, 1956. The preliminary program was published in the March-April DIABETES. Registration for this and previous years is shown in the following table.

	Active Members	Guest physicians	Other guests	Total
1956				
Chicago	406	130	29	565
1955				
Atlantic City	408	137	35	580
1954				
San Francisco	199	99	16	314
1953				
New York	438	198	7	643
1952				
Chicago	325	102	5	432
1951				
Atlantic City	342	125	10	477
1950				
San Francisco	162	83	6	251

THE SCIENTIFIC SESSIONS

Fourteen scientific papers were presented, and twenty-nine were read by title. "Unstable Diabetes" and "Vascular Disease," two panel discussions, were held. Participants in the first were Alexander Marble, M.D., Robert L. Jackson, M.D., E. Paul Sheridan, M.D., George M. Guest, M.D., and Garfield G. Duncan, M.D. The second panel included Arthur R. Colwell, Sr., M.D., Bernard Becker, M.D., Philip M. LeCompte, M.D., Forrest E. Kendall, Ph.D., and Louis K. Alpert, M.D.

Of particularly timely interest were two papers dealing with the oral antidiabetic sulfonamide compounds presented on June 10 by W. R. Kirtley, M.D., A. S. Ridolfo, M.D., Ph.D., M. A. Root, Ph.D., R. C. Anderson, D.Sc.; and by Robert W. Cox, M.D., Elaine D. Henley, M.D., Emily B. Fergus, M.D., and Robert H. Williams, M.D. These papers appear in the current issue of DIABETES.

The Banting Memorial Lecture was delivered at the Scientific Session on June 9 by William C. Stadie, M.D., Professor of Research Medicine, The John Herr Musser Department of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. His lecture, entitled "Recent Advances in Insulin Research," was published in the July-August issue of DIABETES.

The Annual Banquet, June 9

ADDRESS OF THE PRESIDENT
Henry T. Ricketts, M.D.
Chicago, Illinois

"WHERE, OH WHERE WILL THE MONEY COME FROM?"

My first obligation is to trace the derivation of my title. Its meaning is plain enough, but why the poetic verbiage? When one wishes to give point to his message, or perhaps soften its impact when it is concerned with subjects somewhat less than romantic, one quotes the classics. True to this tradition, but surpassing the mine run of orators in the purity of my source, I should like to take you back to the era of F. Scott Fitzgerald and the music that was prevalent in that day, the heyday of jazz. In the 1920's there was a song, not written by Fitzgerald, that went like this:

"How could little Red Riding Hood
Have been so very good
and still keep the wolf from the door?
Mother and Father she had none,
So where, oh where did the money come from?"

Anyone low-minded enough to deduce that Little Red Riding Hood was being kept by a boy friend is perfectly right. But this is a digression. What I want to know is, where, oh where will *our* money come from?

I must tell you at the outset what pleasure it is to speak on a topic—fund raising—that has endeared itself to me by reason of long acquaintance. Its introduction at each session of the Council is eagerly anticipated, year after year; and the exposition of the same issues, phrased in the same way by much the same people, has recurred so often that an atmosphere of ritual has developed about this item of the agenda. It is something without which we should be lost and incomplete. One might infer from the frequency with which the subject comes up that there are differences of opinion about it. I would have you know that unanimity prevails in our Council, in this matter as in many others. The protagonists of our present policies are unanimous on their side, and the antagonists on theirs.

That I could have chosen a more inspiring subject for a presidential address will hardly be challenged. I believe it is my duty, however, to explain the financial dilemma of the ADA and to trace the steps that have led to it.

We think we need more money. Why?

Primarily for a modest expansion of our activities. Such expansion would be in response to demands that are already being felt; not the result of imagined needs or of a desire to grow bigger in the belief that success is proportional to size. The demand, of course, is partly of our own making, but most of it was there in the beginning. It took the vision of our founders to see that the interests of diabetic patients would be served by a formal organization devoted to their welfare. It required much thought and planning by early Councils to determine *how* those interests could best be served. As our program grew and found not only acceptance but success, calls for our services increased; and as these increased, the costs of meeting them did likewise. Fortunately, up to this point, and not entirely by accident, revenues have kept pace with expenses, in large measure because of the great generosity of a handful of donors. Further growth, and growth is inevitable, will outstrip present resources, and new ones will have to be found. Some of our activities, particularly our publications, are essentially self-supporting, but others are far from it and will probably remain so. I refer to public education and case finding (please note the order in which these are expressed), patient education aside from FORECAST, professional education over and above the journal DIABETES, and especially research. It is evident to anyone familiar with our crowded and overworked office that any increase in these programs will require some additional space and staff.

I repeat, we are not deliberately seeking new fields to conquer. It is just that the old fields are getting larger.

Just how much hard cash it will take to provide for the reasonable and healthy growth that I think it to be our lot is anybody's guess. Our income for the past year was approximately $250,000. On that basis, my own estimate is that we shall need annually from $100,000 to $150,000 more than this by 1961.

Not only does the Association need *more* money, but it must pay close attention to *what kind* of money it receives. By this I mean, of course, what are to be its sources of support? In this connection, I must call your attention to an important and somewhat disturbing fact, of which I have already given some hint. Today, 40 per cent of our total income is unearned income, and of this, nearly 90 per cent is derived from a few large contributors. This is a precarious situation. These particular pillars of our financial structure are mighty but few, and

the effect of removing even one or two of them could be disastrous. Most of them, if not all, should be replaced as soon as possible by many small pillars, so that the loss of a few here and there would not matter much. We should, in other words, broaden our base. For this purpose the Association must contrive to raise at least $75,000 per year from individuals, largely, whose annually recurring contributions can be counted upon as a dependable source of income, replacing a substantial share of the present gifts from corporations.

Lest these remarks be construed as ingratitude toward our large benefactors, I hasten to say that without them this Association could not have reached the place where it stands today. They have contributed not only funds but also services and even personnel of inestimable value, and our Association is greatly in their debt. Unless I read the signs wrongly, however, these same benefactors will be among the first to cheer the day when we can say to them, to quote one of my distinguished predecessors, "Thanks, Uncle, for all you have done to rear us. We have long pants now, we have grown up, and we think we can stand on our own feet."

I have said that we need to attract considerable sums from many small contributors. A logical source of such contributors would be individuals with diabetes, those for whom the Association was founded and who reap the benefits of its activities. The problem is how to reach them. A start has been made by appealing in each issue to the subscribers to FORECAST. The results thus far are surprisingly good, some $10,000 having come in during the past year from this source, and the rate is steadily increasing. Nevertheless, even with the growing circulation of this magazine, now about 40,000, it is obvious that we can reach only a small fraction of the two million diabetics who are potential contributors.

Under these circumstances, the possibility of contacting diabetics through the Affiliate organizations has naturally suggested itself. The only feasible way of doing this would be to ask the Affiliates to raise as much money as they can from the diabetics in their respective areas and to remit a portion of their "take" to the national organization. In effect, then, the Affiliates would be contributing to the support of the parent body, as is the custom in most *voluntary health* agencies.

The difficulty is that the Affiliates have already solicited all the diabetics they can lay their hands on, and this source of revenue has been insufficient for their own local needs, let alone a contribution to the ADA. Even when fund-raising efforts have been directed toward the families and friends of diabetics, and with a very liberal interpretation placed on the word

HENRY T. RICKETTS, M.D., PRESIDENT, 1955-56

"friends," many of the Affiliates have had inadequate funds to carry on a strong program, and some cannot afford the minimum perquisites of a regular office, a paid secretary and the usual telephone, stationery and stamps. A recent survey showed that of thirty-seven Affiliates, twenty-one had budgets of less than $1,000. This does not add up to anything like a gold mine for the ADA.

The question is, then, how can the Affiliates raise more money, principally for their own requirements but also for a modest contribution to the national organization? They have been operating, as you know, under a policy adopted by the Council that does not favor general public fund raising. In keeping with that policy, the Council has had prepared and distributed to Affiliates a fund-raising manual that describes in great detail acceptable methods of raising money short of the use of appeals through newspapers, radio, television and the like. How successful this will be remains to be seen. If the skeptics are right, and there are many of them, the Affiliates will have little choice but to go to the public at large.

At this point, I believe you are entitled to know something of the evolution of the Council's thinking about general public fund raising. The Council has defined general public fund raising as raising money

from the public at large by means of the media of mass communication, i.e., newspapers, radio and television, in addition to canisters, car cards, theaters, door-to-door solicitation and similar devices. Why has the national organization not embraced such a program?

First, we are an organization of physicians, and we have feared that, if we were to stage a nation-wide drive for money each year, it would lead eventually to lay control. This, without exception, has been the history of all the large voluntary health agencies. If the public contributes, it will demand and deserve a voice in decisions as to how the money is spent.

Second, we have wanted to avoid the ballyhoo, the spectacle, the tear-jerking technics and the appeals to fear that have variously characterized many money-raising ventures in the health field. I am happy to say that these undesirable features are less prominent than a few years ago. They were the work of well intentioned, enthusiastic but misguided lay groups and their professional publicists. This is one of the reasons for our determination to keep our Association in the control of physicians.

Third, by refraining from national public fund raising, by refusing to join the almost endless parade of appeals for special diseases, we have attained a unique and respected position which we are reluctant to give up. Once we abandon this position we can never regain it. It would be an irreversible step.

For these reasons, and others, the Council has steadfastly resisted the temptation to commit the American Diabetes Association to a policy of general public fund raising.

The question now arises, do the arguments that have deterred the national organization apply with equal force to the Affiliate organizations? Insofar as the governing bodies of the Affiliates are clinical societies, and there are few exceptions, the answer is yes. The retention of professional control would seem to be as important at the local level as at the national, and for much the same reasons.

There are additional considerations. General public fund raising tends to create an attitude of mind that makes money an end in itself, so that the goals for which money is needed grow dim. Time on radio and television, the most effective means of mass communication, is expensive. Would the returns justify the outlay? Would the diabetic get as much per dollar spent as he now gets? It should be remembered, too, that diabetes does not have the dramatic appeal of infantile paralysis and cancer or the quantitative appeal of heart disease. How responsive would the public be?

On the other hand, we have been aware of the possibility that hard necessity may override these objections. Perhaps diabetics, their families and friends, even when contributing at maximum feasible capacity, cannot supply enough to meet the needs of the Affiliates and their parent body. Probably more money can be raised with less effort, or with fewer workers, by the use of mass media. The St. Louis group think so, and they think they have reached more diabetics, not to mention the general public, in this way than by limited fund raising technics.

Finally, the relationship of Affiliates to United Fund Campaigns and Community Chests presents a knotty problem. There are some Affiliates which, if they wish to raise any considerable amount of money locally, must participate in such movements, and there are others that wish to. Since these agencies indulge in general public fund raising, Affiliates that join them run counter to the policies of the American Diabetes Association as defined until now, and the ADA in turn cannot accept from Affiliates money that is obtained by such methods, no matter how dignified these may be. The growing resentment against multiple financial drives is leading to an increasing prevalence of United Funds and Community Chests throughout the country, and to the extent that these multiply, to that extent will be augmented the embarrassment of the affected Affiliates and the national organization. There is, however, the complication that some cities in which funds are raised by public subscription will not permit their diversion to national headquarters. Where does that leave papa?

These, then, are some of the problems. The easy solution would be for the ADA to go frankly into general public fund raising on a nation-wide scale, thus providing funds for both itself and its Affiliates. The Council, for the reasons I have given, is still unwilling to alter so drastically the character of our Association.

So, you say, "What do *you* propose?"

As a prelude to my answer, let me say that I believe the objectives of the American Diabetes Association will be mostly broadly realized through its affiliated organizations. These must be strengthened beyond their present struggling condition. Their greatest weakness is lack of funds with which to carry out their own programs, which, in the main, are but smaller versions of the national program. Therefore, if general public fund raising at the local level is what is needed to strengthen the Affiliates, and the great majority of them think this is true, I believe, in company with many of the Council, that it should be permitted, with the help

and guidance of the national body. Fund-raising activities would have to be conducted with complete honesty and dignity, and departure from such principles should involve forfeiture of affiliation. With the Affiliates thus provided, hopefully, with a more promising source of income, their own effectiveness would be increased, and at the same time they could, and should, make some contribution to the parent organization.

To these proposals, the objection will be raised that, if the Affiliates are permitted to engage in general public fund raising, the national organizations will be tarred with the same brush, since the Affiliates are, by definition, our relatives. The truth of this is granted, but some compromise seems unavoidable. At any rate, by refraining itself from general public fund raising the ADA makes certain that its affairs remain in the control of physicians and maintains its freedom to alter or modify fund-raising policies in accordance with changing requirements.

It will be further objected that for the Affiliates to engage in general public fund raising while the parent body sits by with folded and relatively clean hands is like making your children beg for you because you are too proud to do it yourself. The answer to that is that the great majority of Affiliates *want* to engage in this sort of activity; and as for begging, the ADA is already expert at this game and intends to go on playing it, but in its own way.

As one who has long disapproved of general public fund raising in any form, I have come to these conclusions reluctantly. Having stated them, I must now prepare to resist alike the blandishments of those who will rise up and call me blessed, and the caviling of those who will call me damned.

If our peculiar brand of unanimity is any guide, there will be plenty of both.

As a postscript, which could not have been added until today, I must inform you that the Council, at its meeting yesterday, took action modifying our fund-raising policies along the lines I have just indicated. For this I can take no personal praise or blame, having gone to some pains to keep my opinions to myself.

PRESENTATION OF CITATION

Following the Address of the President a citation was presented to Mrs. Earl R. Hoover, Vice President, The Diabetes Association of Greater Cleveland, by Edwin W. Gates, M.D., Chairman, Assembly of Delegates, American Diabetes Association. The citation reads: "In recognition of her devotion to the well-being of diabetics in the City of Cleveland and her outstanding efforts in the development of The Diabetes Association of Greater Cleveland, the American Diabetes Association awards this Citation to Alice Propst Hoover. (Signed) Franklin B. Peck, Sr., M.D., Secretary; Henry T. Ricketts, M.D., President."

THE BANTING MEDALS

Banting Medals were presented to: William C. Stadie, M.D., as the Banting Memorial Lecturer, by Henry T. Ricketts, M.D., President; to Louis Harry Newburgh, M.D., in absentia, by Dr. Ricketts; and to Henry T. Ricketts, M.D., as retiring President, by Henry B. Mulholland, M.D., immediate past President. The response by Dr. Cecil Striker on behalf of Dr. Newburgh, who is now deceased, follows.

REMARKS BY DR. CECIL STRIKER FOLLOWING PRESENTATION OF THE BANTING MEDAL TO DR. L. HARRY NEWBURGH, IN ABSENTIA

Mr. President, Officers of the Association, Ladies, Distinguished Guests and Colleagues:

I stand here with mixed emotions, very much distressed that Dr. Newburgh cannot be here to receive the Banting Medal, but very much honored to have been asked to receive it on his behalf.

Dr. Newburgh came originally from Cincinnati and after having graduated from Harvard Medical School in 1908, practiced in Cincinnati briefly before returning to academic life. He had been away for a number of years and I had not known him in Cincinnati.

My association with Dr. Newburgh dates back to 1924 when I received an appointment to work with him at the University of Michigan. Indeed, those were the days; there was very little insulin available and almost all diabetic patients were living on an undernutritional diet. Dr. Newburgh was convincingly demonstrating that nitrogen equilibrium could be maintained and ketosis controlled by putting patients on diets very low in carbohydrates and low in protein but high in fat. For example, the Newburgh Four, as it was called in those days, was a diet of 35 gm. of carbohydrate, 55 gm. of protein and 220 gm. of fat. Many were the potato

farmers of Michigan, who lived successfully on this diet and were able to carry on their daily responsibilities before the wide use and availability of insulin. Although these diets dripped with fat, all of us at that time had the daily experience of seeing many diabetics able to carry on under such a regime.

It is not my assignment to outline Dr. Newburgh's scientific activities, although I could have spent considerable time doing so. Instead I have been asked to speak, and I quote Dr. Ricketts, "A few informal remarks, to occupy not more than five minutes, and pertaining more to your personal contacts than with Dr. Newburgh's scientific accomplishments." The scientific accomplishments are a matter of record but the personal interchange is hard to document. However, it is often through the spoken word that the intangible qualities of an individual are transmitted. I shall never forget when I first arrived on his service that he arranged for a stall for me at the University of Michigan Library and said in a rather casual fashion, "I would suggest that you go through Benedict's *Human Vitality and Efficiency under Prolonged Restricted Diet* (which is seven hundred and one pages) and after you have gone through this, possibly we could discuss it." Further, I shall never forget the daily rounds at the old University Hospital where along with the human interest in the patient, Dr. Newburgh led a very objective discussion of the chemical phenomena that were going on in that patient. As every investigator exemplifies an unsatisfied individual, so Dr. Newburgh always propounded the eternal question of why, why, why. It was my great privilege to be quite closely associated with him daily and although I believe that he demonstrated the most objective point of view in trying to understand mechanisms, there were other facets of his personality that warmed one to him. He had a delightful sense of humor and enjoyed participating at home in the daily chores such as washing dishes and building fences and at an informal gathering could often be found seated on the floor in the midst of a heated discussion. Above his objectivity and warmth of personality, however, there was an outstanding trait, namely, humility. He was always surprised when anyone praised him. After he had taught for thirty-six years, a dinner was given in his honor upon his retirement. I shall never forget the remark he made to me when I went from Cincinnati to Ann Arbor for the occasion. "Gosh," he said, "you came all the way up here for this!"

Every medical school has its great characters. Some seem to be so identified with the place that when we read or learn of their retirement, it is hard to grasp because we have come to think of them as being almost immortal. For more than thirty-six years Dr. Newburgh taught at Ann Arbor, during which time thousands of students passed under his tutelage. I am sure that from each one he drew unqualified admiration, devotion and affection. He was not only a superb teacher whose enthusiasm for metabolic diseases was infectious, but also was one of the most courteous gentlemen one could ever wish to meet. To those who were finding the going too rough, his appearance on the scene was always a relief, because he could restore order from chaos, remarking in an inimitable way, "This is the mechanism."

His influence extended far beyond the University of Michigan through the medium of his students, who were imbued with his ideas and ideals, through his publications and active personal participation in scientific meetings.

Few men have given longer service more humbly and few can have had a greater influence for good over such a large number of men. I am sure the diabetic population of the world has been enormously benefited as the direct and indirect result of Dr. Newburgh's teaching. In his later period he became interested in renal diseases and made another important contribution to this field of medicine. But that is another chapter.

It is with mingled pride and humility that I accept the Banting Medal on behalf of Dr. Newburgh.

Annual Business Meeting

The Annual Business Meeting of the Association was held June 10. The remarks of Henry T. Ricketts, M.D., President, were followed by reports of the Secretary, Treasurer, Executive Director, and the Chairman of the Nominating Committee.

Remarks by the President

The first scheduled item in the business session is remarks by the President. I should like to report briefly that the Association is undergoing a normal, healthy growth. The year has been marked by a number of important developments, not the least of which is the retirement of the original Editor of DIABETES and his replacement by Dr. William C. Stadie as Editor and Dr. Irving Graef as Associate Editor.

Committee activities have been going on vigorously.

A new committee has been established, entitled the Informational Committee on Oral Antidiabetic Compounds. This will be a source of information for professional members of this Association as well as the laity through the lay magazine FORECAST.

The Committee on Research and Fellowships has awarded three fellowships during the past two years to recipients of very high caliber.

The Committee on Employment has done an excellent survey of practices in industry concerning the employment of diabetics, and their report will be published in our journal.

The Committee on Camps has come up with a set of minimum medical standards for camps which will be of help, I am sure, to the camps for diabetic children throughout the country.

The work of the Committee on Scientific Programs needs no comment. I should like personally to commend that Committee, and its Chairman, Dr. John A. Reed, for the excellence of the program which they have put on at this meeting.

Our publications are all going strong, and are in a healthy financial situation. These are the journal, DIABETES; the lay magazine, FORECAST; a new and very popular publication, *Facts about Diabetes*, designed primarily for the general public but also for diabetic patients; and finally, *Diabetes Guide Book for the Physician,* the revised edition of which is in page proofs and will soon be released.

Perhaps the most important development that has occurred has taken place within this past week, namely, the modification of the fund-raising policy of the Association to permit general public fund raising on the part of Affiliate organizations. This most of you heard, I think, last night at the banquet. This action puts a different complexion on this Association from that which it has worn since its founding. I should like to admonish the members of this Association that this move could possibly lead to a considerably different kind of control in the local Affiliates of the ADA unless physician members are determined to retain that control in their own hands. This may take some watchdog activity. I hope it will be exercised.

For the coming year, there are two principal problems. The first is the appointment of a field representative, whom we have been looking for, as a matter of fact, and have not yet found. The second, and related problem, is a better and clearer delineation of our Affiliate structure, and the relationship of the Affiliate not only to the national organization but to state organizations and locals within those states. This is a charge which the Committee on Affiliate Associations has received from the Council and to which it will give, I am sure, close attention.

I am asked to report that the move to re-establish a collaborative, cooperative meeting with the Endocrine Society, to which I made reference in yesterday's scientific session, is already under way. Committees have been appointed and are at work on it. I am sure there will be a re-institution of our previous relationship.

I cannot make this report without reference to the excellence of the National Office and to the highly efficient operations of Mr. Connelly and his staff. I marvel each year I see them going about their business, both in the office and in meetings of this kind. I assure you, you could find no better staff, no more loyal or efficient or hard-working people than you have working in the National Office today. They deserve the highest praise and our deep appreciation.

I should like finally to express my own appreciation of the honor you bestowed upon me last year in electing me your President. It has been a great pleasure to serve in this capacity, and I wish to thank most sincerely the Councilors, the Governors, and the Executive Committee for their superb cooperation.

HENRY T. RICKETTS, M.D.

Report of the Secretary

I, too, would like to make a few comments about the general situation in the business conduct of the organization. It has grown steadily over the years as its objectives, professional education, patient education, public education and case finding, and research and fellowships have come closer to fulfillment.

It is noteworthy that the educational aspects of this program have now reached the dominant position and actually absorb the major portion of the time and the effort of the central office.

Your office in New York now requires the services of about twenty people, and a considerable amount of additional work must be farmed out. This office is the clearing-house for all the innumerable details involved in the work of five officers, twenty-five working committees, composed of two hundred of your members, in addition to the thirty-nine Affiliate organizations, the Assembly of Delegates, the Board of Governors and the Council.

It also publishes DIABETES and FORECAST and other publications which Dr. Ricketts mentioned, all of which is a sizeable publication undertaking in itself. To the question proposed by Dr. Ricketts last night, "Where does the money come from?", I would like to add an-

other. "How do these people do it?" Over three hundred letters and communications go out of the office per day. There are three trunk lines leading in there, and you never can get a telephone line. I know that the Executive Director often spends six hours in a day answering that telephone. The bill for telephones now runs over some $300 per month. The answer to my question lies in the devotion of this staff of dedicated people that our Executive Director has assembled, including Mr. Connelly himself. I, too, want to take this opportunity of expressing our thanks to all of them.

The 1957 Postgraduate Course will be held in Columbus, Ohio, on January 30 to February 1. Plans are being negotiated for courses from 1958 to 1959, probably in Atlanta and St. Louis respectively.

The next Annual Meeting will precede the American Medical Association Meeting in New York, and it is hoped that arrangements for better correlation with the Endocrine meeting can be established.

Our membership continues to grow, showing a net gain of 76 members during this year. There are now Honorary Members, 13; Active Members, 2,117; Associate Members, 46; and Corporate Members, 25, with a total of 2,201. Thank you.

FRANKLIN B. PECK, SR., M.D.

Report of the Treasurer

It is a pleasure to report an increase in the income of the Association for 1955-56. The total is $259,459.41 with $8,887.45 of this amount restricted as to its use. Of the total income received, $106,145.52 was derived from our publications, DIABETES and ADA FORECAST; from Corporations, $88,550.00; from FORECAST readers, $9,960.86; from Foundations, $12,350.00; and the balance of $42,453.03 from Membership Dues, miscellaneous contributions, interest on savings, and sales of booklets and reprints. Every item of our income shows an increase over 1954-55. This is very gratifying to say the least.

Our total expense for 1955-56 is $232,487.45, with $6,003.00 of this amount representing Fellowship stipends, deductible from our Restricted Funds. Net Income over Expense was $26,971.96.

Our earned Income, that is income exclusive of large corporate and Foundations gifts, is 61 per cent of the total. It is the opinion of your Treasurer that the financial condition of the Association is sound and that, as our Affiliates add to the yearly income such contributions as they can, we shall steadily approach a yearly recurring income from sources within the Association. Further, your Treasurer expects the Corporations, which have and do contribute so generously, to continue to do so. Thus we may expect to have available more funds for research and other needed projects the Council has considered, but for which funds are not now available.

WILLIAM H. OLMSTED, M.D.

Report of the Executive Director

Dr. Ricketts, Dr. Peck, Dr. Olmsted: I want to thank all of you for your kind words about the staff and myself. We consider it a real privilege and honor to serve the Association. Although the agenda indicate that this is to be a report, time does not permit, which perhaps is fortunate for all of you. However, I do want to take this opportunity to greet each one.

Through correspondence and various meetings, I have felt that I was acquainted with you. However, last night's reception made me realize—to my embarrassment, I might add—that I only thought I knew the names of all Association members. The very nature of a national organization makes it impossible, I suppose, to be acquainted personally with all the members. I wish it were otherwise.

The change in policy adopted by the Council at this meeting which permits Affiliates to engage in general public fund raising, I am sure will present many problems. To those of you who are members of Affiliates, I would personally like to urge conservative campaigns if your Affiliate decides to enter into this kind of activity, and wait until the National Organization has had an opportunity to set forth certain principles and guides. Although the Council did not intend for the parent organization to become engaged in various campaigns themselves, we will try to provide whatever counsel is necessary.

In closing, I would like to say—as I did last year and the year before—that the American Diabetes Association is an organization of individual members. All members have the same rights and privileges and that is the principle upon which the National Office functions.

It is a great pleasure for me to be associated with the organization, and I enjoy working with everyone. For the staff and myself, I wish to extend to each one of you a very cordial invitation to visit us at the National Office at any time.

Meanwhile, for those of you who are not planning to be in New York in the near future, I will be in the back of the room or in the foyer, and I would be delighted to talk to you any time this afternoon. Thank you.

J. RICHARD CONNELLY

Resolution by George F. Schmitt, M.D.

The following resolution was offered by Dr. Schmitt, Miami, Florida.

"Whereas, the current scientific presentation of the American Diabetes Association at the American Medical Association Annual Session is almost solely the work of the Chairman of the Committee on Scientific Exhibits, Dr. William R. Kirtley, of Indianapolis, who has also served with great diligence during the past four years,

"Therefore be it resolved: That the membership of the Association take this means of expressing to him their appreciation of his efforts."

This resolution was seconded by Edward L. Bortz, M.D., Philadelphia, and was adopted by acclaim.

Report of the Nominating Committee

We have attempted to make recommendations while promoting the objectives of the Association in all fields. We propose for nomination men who have shown capacity for service to the Association through work on the committees of the National Organization, through leadership of Affiliates, and through participation in the scientific programs.

We made our selections purely on the basis of merit, and on reviewing the prospective composition of the Council, were pleased to find a well-balanced representation of different interests, practice, teaching and research. And also, a well-balanced geographical representation.

On behalf of the Committee, I move the nomination of the following:

For President: Dr. Frederick W. Williams, of New York; for First Vice President, Dr. John A. Reed, of Washington, D.C.; for Second Vice President, Dr. Alexander Marble, of Boston; for Secretary, Dr. Franklin B. Peck, Sr., of Indianapolis; for Treasurer, Dr. William H. Olmsted, of St. Louis.

For Councilors for the term ending in 1959: Dr. Louis K. Alpert, of Washington, D.C.; Dr. W. Wallace Dyer, of Philadelphia; Dr. Edwin W. Gates, of Niagara Falls; Dr. Harvey C. Knowles, Jr., of Cincinnati; Dr. Arnold Lazarow, of Minneapolis; Dr. E. Paul Sheridan, of Denver.

(It was moved, seconded and voted that the nominations be closed. The nominees included in the report of the Nominating Committee were duly elected.)

Since the election of Dr. Marble as Second Vice President leaves a vacancy in the Council, we nominate Dr. Arthur R. Colwell, Sr., of Chicago, to fill his unexpired term expiring in the class of 1958.

(It was moved, seconded and voted that the nominations be closed. Dr. Colwell was duly elected.)

FRANK N. ALLAN, M.D., *Chairman*
RANDALL G. SPRAGUE, M.D.
HENRY B. MULHOLLAND, M.D.

Installation of incoming President

HENRY T. RICKETTS, M.D., *retiring President*: Now it becomes my duty to transfer the responsibilities and pleasures of my office to Dr. Frederick W. Williams of New York.

Dr. Williams was a member of the organizing committee of the American Diabetes Association and a member of its first Council. He has been a member of practically every committee that the organization has had at one time or another so that he is thoroughly familiar with our structure and our policies, and he knows his job, I am sure, very well.

As you know, he is the present Editor in Chief of FORECAST, and a regular contributor to it.

He was the Chairman of the Committee on Scientific Programs in 1955, and of course, has just completed his term as First Vice President.

Dr. Williams' realism, of which he has plenty, his knowledge of medical organizations and of the intricacies of parliamentary procedure, and above all his loyalty to the American Diabetes Association, have made him a valued member of our Council.

These attributes, and many others which I don't have time to mention, will render him a highly effective leader of this Association in the coming year.

Dr. Williams, I am pleased to transfer to you the official gavel of the Association.

Address of the newly installed President

Mr. most recent past President and Members: For once in my life, I am speechless!

I don't have to tell you what this means to me. It's a great pleasure and an honor. It is something I had hoped that some day might happen, and I am glad it has taken this long until it did, because it gave me that time to serve and be trained. In the early days little did we think that the organization would ever grow to the extent that it has.

When we all sing the praise of the office staff and Dick Connelly—you all heard the Treasurer's report. How do they do it? Yet, the work always gets done. I regard it as a privilege and an opportunity to serve as President of this unique organization.

I regard it as a high honor, and of course, I approach it with humility, but with the utmost confidence because I am due to serve an apprenticeship of one year under

the Master Magician, Dick Connelly.

FREDERICK W .WILLIAMS, M.D.

COUNCIL SESSION

Recommendations of the Committee on Policies

The following is a restatement of the fund-raising policies of the American Diabetes Association, as it was accepted by the Council at its meeting on June 8.

1. It is recommended that the American Diabetes Association continue its policy of not engaging in general public fund raising at the national level.

2. It is recommended that the American Diabetes Association withdraw its opposition to general public fund raising by an Affiliate provided its clinical society or medical advisory group considers it essential in the local situation, and approves the methods employed, and provided further that such activities be restricted to the geographical area as defined in the terms of its affiliation. Further, the advice and counsel of the national Association will be available and the Affiliate will be expected to act in accordance with the objectives, principles and policies of the American Diabetes Association.

3. It is recommended that the American Diabetes Association will welcome appropriate contributions from the Affiliates to further the objectives of the Association.

4. It is recommended that the American Diabetes Association reserve the right to terminate the affiliation of any Affiliate employing fund-raising technics that are unethical, undignified, or otherwise unacceptable to the national Association.

5. It is recommended that a committee be appointed to draw up means of giving advice and counsel to Affiliates employing, among other means, a revision of the *Fund Raising Manual for Affiliate Diabetes Associations of the American Diabetes Association.*

6. It is recommended that the implementation date of supplying advice and counsel as provided in Recommendation Number 5 be Jan. 1, 1957.

It was suggested that the committee referred to in Recommendation Number 5 be a joint committee appointed from the Committee on Finance and the Committee on Policies.

The Committee on Fund-raising Criteria has been appointed from the membership of the Committee on Finance and the Committee on Policies to study the revision of the Manual referred to in Recommendation Number 5. Affiliates have been urged to hold in abeyance any plans for public fund-raising campaigns pending receipt of the revised Fund Raising Manual, *which will be changed in accordance with the foregoing recommendations of the Commitee on Policies.*

FREDERICK W. WILLIAMS, M.D., President

Committees, 1956-57

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NOMINATING

Randall G. Sprague, Chairman
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Dwight J. Ingle, Maurice Krahl, by invitation, Rachmiel Levine, Henry T. Ricketts

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DELEGATES TO THE NATIONAL HEALTH COUNCIL

Alexander Marble, Herbert Pollack, J. Richard Connelly

SEVENTEENTH ANNUAL MEETING

As previously announced, the Seventeenth Annual Meeting of the American Diabetes Association will be held in New York City, June 1-2, 1957, immediately preceding the Annual Session of the American Medical Association, June 3-7. The Hotel Commodore will serve as headquarters and room reservation cards will be mailed to all members with the announcement on or about November 1.

Scientific Program

Physicians and other scientists are invited by Alexander Marble, M.D., Chairman of the Committee on Scientific Programs, to submit abstracts, not to exceed 300 words in length, of papers which they would like to present at the Scientific Sessions. Those interested are requested to submit eleven copies of the abstracts to expedite review by the Committee. A questionnaire asking for suggestions as well as abstracts of papers to be presented will be sent to all members along with the aforementioned announcement on or about November 1.

FIFTH POSTGRADUATE COURSE

The Fifth Postgraduate Course in Diabetes and Basic Metabolic Problems will be held at The Ohio State University in Columbus, Ohio, Wednesday through Friday, Jan. 30-Feb. 1, 1957. The full program of the Course, which is offered by the American Diabetes Association, will be mailed to all members of the Association in the near future, and will be published in the November-December issue of DIABETES.

George J. Hamwi, M.D., Columbus, is Course Director, and Thomas P. Sharkey, M.D., Dayton, Associate Director. The Deshler Hilton Hotel will serve as headquarters, but all lectures will be held at The Ohio State University.

The program includes papers to be presented on the following major topics: "Pathophysiology of Diabetes Mellitus," "Diagnosis of Diabetes Mellitus," "Clinical Management of Diabetes Mellitus," "Oral Hypoglycemic

Agents," a panel discussion on "Objectives of Treatment in Diabetes Mellitus," "Conditions Complicating Diabetes Mellitus," and "Chronic Complications of Diabetes Mellitus." Luncheon panel discussions have been arranged for each day.

A Social Hour and Banquet will be held on Wednesday evening, January 30. The Social Hour is by individual subscription; registrants and faculty members are guests of the American Diabetes Association at the Banquet. A humorous address entitled "Public Relations and the Physician" will be given at the Banquet by Dr. Russell B. Roth of Erie, Pennsylvania. The internationally known Ohio State University Symphonic Choir will also entertain. A Social Hour will be given on Thursday, January 31, at 6:30 p.m., to which all registrants and their wives are invited.

Those who plan to attend the Course are urged to register as soon as possible. All inquiries and applications should be addressed to the National Office of the American Diabetes Association.

LILLY AWARD

The following stipulations govern the contest for the annual Lilly Award, supported by Eli Lilly and Company and consisting of $500 and a gold medal. The first award will be made at the Seventeenth Annual Meeting, June 1-2, 1957.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training, and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to January 1 of the same year of the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on the subject of his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or the Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the gold medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

NOVEMBER 15 RESEARCH FELLOWSHIP DEADLINE

The Committee on Research and Fellowships of the American Diabetes Association plans to award at least one Fellowship for the academic year 1957-58. The deadline for applications is Nov. 15, 1956. Requests for application forms and other inquiries should be addressed to Mr. J. Richard Connelly, Executive Director, who will forward the information to the Committee.

1956-57 MEDICAL STUDENT-INTERN ESSAY CONTEST

The fifth Medical Student-Intern Essay Contest, open to medical students, interns and physicians within two years after their graduation from medical school, is sponsored by the American Diabetes Association. Any subject relating to diabetes and basic metabolic problems may be selected.

A prize of $250 to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation, has been made possible once again through the kindness of the St. Louis Diabetes Association. An award of $50 will be given for the best review article or case report.

Members of the American Diabetes Association and subscribers to DIABETES are requested to encourage medical students and interns to enter the contest.

The papers will be judged on the basis of value of the material and method of presentation.

Entrants should submit the original and one copy of their manuscript (four additional copies would be appreciated). The manuscript should be typewritten and double-spaced, and mailed by April 15, 1957, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

NEW MEMBERS

Active

The following were elected as of Aug. 1 and Sept. 1, 1956:

California
Winsor, William G., III — Whittier

Delaware
Briggs, Ward Wright — Wilmington
Hall, William T. — Wilmington
Kimble, Leroy R. — Wilmington
Klingel, Robert L. — Rehoboth Beach
Resnick, Elton — Wilmington
Rovitti, Francis P. — Wilmington

Florida
Bogdonoff, Morton D. — Miami
Stannus, Donald G. — Miami

Illinois
Bruch, Ernest — Rockford
Koven, Arthur J. — Maywood
Wu, Jackson S. — Chicago

Indiana
Lewis, George N. — Gary
Ridolfo, Anthony S. — Indianapolis

Iowa
Coulson, Forest H. — Burlington

Louisiana
Haspel, Robert B. — New Orleans
Voorhies, Norton W. — New Orleans

Maryland
Connor, Thomas B. — Baltimore
Weiger, Robert W. — Bethesda

Michigan
Adelson, Seymour S. — Detroit
Hailman, Harold F. — Kalamazoo
O'Donovan, Cornelius J. — Kalamazoo

Minnesota
Johnson, Morris B. — Minneapolis

Missouri
Black, Don A. — Kansas City
Goldenberg, Sidney — St. Louis

Montana
Schultz, Donald O. — Helena

New Jersey
Remsen, Douglas B. — New Brunswick

New York
Argue, John F. — Wilson
Mallo, Joseph P. — Niagara Falls

Ohio
Craig, James W. — Cleveland
Sondheimer, Martin M. — Lima
Wilson, Donald C. — Toledo

Pennsylvania
Ayerle, Robert S. — Levittown
Mayock, Peter P. — Sayre
Pauley, William G. — Levittown

Washington
Kyle, Robert A. — Seattle

Other Countries

Cuba
Mateo De Acosta, Oscar — Havana

Mexico
Hernandez C., Julio A. — Mexico City, D.F.

Associate

The following was elected as of Sept. 1, 1956:

Connecticut
Sullivan, Patricia E. — New Haven

NEWS OF AFFILIATE ASSOCIATIONS

The DIABETES COUNCIL OF THE PUBLIC HEALTH FEDERATION OF CINCINNATI, an Affiliate Association, has established the William H. Muhlberg Lecture in cooperation with the Cincinnati Academy of Medicine and the Union Central Life Insurance Company. The William H. Muhlberg Fund, to be administered by the Public Health Federation, has also been established.

The lecture was named after Dr. Muhlberg, first treasurer of the American Diabetes Association, in recognition of his outstanding contributions in diabetes. It is to be given biennially as the joint meeting with the Academy of Medicine by an eminent teacher, clinician or investigator. The first William H. Muhlberg Lecture will be presented by Francis D. W. Lukens, M.D., Philadelphia, on November 20 this year.

The NEW ENGLAND DIABETES ASSOCIATION held its Annual Meeting on June 19 at Smith House, Cambridge, Massachusetts. The scientific section of the meeting consisted of summaries of outstanding papers given at the Sixteenth Annual Meeting of the American Diabetes Association. The summaries were presented by Frank N. Allan, M.D., Reed Harwood, M.D., Alexander Marble, M.D., and Samuel B. Beaser, M.D.

The NEW JERSEY DIABETES ASSOCIATION in cooperation with the New Jersey State Department of Health will present The Fourth Annual Symposium on Diabetes Mellitus on Wednesday, October 17. The program will be given at the Academy of Medicine of New Jersey, 91 Lincoln Park South, Newark. Otto Brandman, M.D., President, New Jersey Diabetes Association, will open the symposium. Introductory remarks will follow by Louis C. Fritts, M.D., President, The Medical Society of New Jersey. These papers will be given: "The Im-

portance of Post Graduate Medical Education," by Charles L. Brown, M.D.; "An Evaluation of Diabetes Clinics in New Jersey," by Arthur Krosnick, M.D.; "Carbohydrate Metabolism in the Pregnant Diabetic," by Joseph T. Beardwood, M.D.; "Management of Diabetes in Pregnancy," by Harold Brandaleone, M.D.; and "Present Status of the Sulfonylureas in the Treatment of Diabetes Mellitus," by Franklin B. Peck, Sr., M.D., and Max Ellenberg, M.D. John J. Torppey, M.D., will serve as Session Chairman.

The WASHINGTON DIABETES ASSOCIATION (Clinical Society) in cooperation with The Washington State Health Department and The Diabetes Teaching and Research Foundation presented a Second Annual Symposium on Metabolic and Endocrine Diseases on August 3 in the Health Sciences Auditorium of the University of Washington School of Medicine, Seattle. Lester J. Palmer, M.D., and Charles Olson, M.D., served as Moderators of the morning session which included the following papers: "Clinical Experience with Oral Hypoglycemic Sulfonylureas" by James R. Hendon, M.D., Louisville, Kentucky; "Mode of Action of the Hypoglycemic Sulfonylureas," by Robert W. Cox, M.D.; "New Concepts of Diabetic Retinopathy" by Louis N. Hungerford, M.D.; "The Relationship of the Anterior Pituitary to Diabetes Mellitus," by E. Perry McCullagh, M.D., Cleveland, Ohio; and "The Clinical Effect of Cortical Steroids on Diabetes Mellitus," by Hamish McIntosh, M.D., Vancouver, B. C. The afternoon session, with John Hogness, M.D., and Joseph Crampton, M.D., as Moderators, included: "Evaluation of Adrenal Cortical Function," by Hamish McIntosh, M.D.; "An Appreciation of Hyperparathyroidism: Its Incidence and Detection," by James R. Hendon, M.D.; "Nature and Treatment of Thyroiditis," by E. Perry McCullagh, M.D. The participants in a panel entitled "Presentation of Problem Thyroid Cases: How Would You Handle Them?" were E. Perry McCullagh, M.D., Robert H. Williams, M.D., and Hamish McIntosh, M.D.

NEWS NOTES

DIABETES ABSTRACTS AVAILABLE

The American Diabetes Association has a number of back issues of DIABETES ABSTRACTS available for interested members.

Nearly all of Volumes 1-10 (1942-1951), a five-year cumulative index covering Volumes 1-5 (1942-1946), and a five-year cumulative index for Volumes 6-10 (1947-1951), may be obtained without charge from the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y. Please note that Nos. 2 and 4 of Volume 6 of DIABETES ABSTRACTS are out of print.

PERSONALS

PIERO P. FOA, M.D., Department of Physiology, Chicago Medical School, received a grant of $3,766 for research studies in diabetes from the National Institute of Arthritis and Metabolic Diseases.

ROBERT F. LOEB, M.D., College of Physicians and Surgeons, Columbia University, has been appointed to a special committee of the Ford Foundation. The purpose of the committee is to recommend a formula for allocation among medical schools of the Foundation's $90 million gift.

OBITUARIES

EMANUEL M. ABRAHAMSON, M.D., was born in Brooklyn, New York, in 1897, and died in New York City on March 19, 1956. The author of a book on hyperinsulinism, he wrote many articles on diabetes.

Dr. Abrahamson was graduated with a B.S. cum laude from Columbia University in 1917, and received a Ch.E. degree in 1919, an M.A. in 1920, and a Ph.D. in 1922. In 1926 he was graduated from the College of Physicians and Surgeons, Columbia University. From 1919 to 1922 he served as an assistant in the department of chemistry at Columbia University and as an intern at the Jewish Hospital of Brooklyn in 1926 and 1927. He studied in Berlin and Vienna in 1927 and 1928, and on his return served as an associate in the Diabetic Clinic at the Jewish Hospital of Brooklyn from 1929 to 1939. Dr. Abrahamson was an associate attending in medicine at the Jewish Hospital from 1935 to 1940. A member of the American Diabetes Association since 1941, he was a diplomate in internal medicine.

DONALD RAY BLACK, M.D., was born in Pittsburg, Kansas, in 1889 and died Nov. 3, 1955, at Carrollton, Missouri. He received his A.B. degree in 1914 and his M.D. degree in 1916 from the University of Kansas. From 1919-1923 he served as Assistant Professor of Pathology at the University of Kansas School of Medicine and as Assistant Professor of Medicine from 1923 to 1928. Dr. Black limited his practice to internal medicine, and was on the staff of the Research Clinic of the Kansas University Medical School. A member of the American Diabetes Association since 1941, he was also a member of the American Board of Internal Medicine. During World War I he served as a captain at Base Hospital Number 28.

A VALUABLE LIBRARY

The *Proceedings of the American Diabetes Association,* containing a great body of clinical information of practical use to every physician treating diabetes, may be purchased at a special price of $34.50 for Volumes 2, 3, 4, 6, 7, 8, 9 and 10. Volumes 1 and 5 are out of print. For those who wish to complete their series, separate volumes may be obtained at $5.00 a copy. Please direct your orders to the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

The *Proceedings,* previously published annually, was discontinued in 1950 with Volume 10. The publication was superseded by DIABETES, *The Journal of the American Diabetes Association.*